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THE AMERICAN JOURNAL of HUMAN GENETICS

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The American Journal of Human Genetics

Vol. I No. 1 *September 1949*

Progress and Prospects in Human Genetics

A Preface to this Journal

I. FUNCTIONS OF THE AMERICAN SOCIETY OF HUMAN GENETICS

In December, 1947 an informal gathering was held during the meetings of the American Association for the Advancement of Science at Chicago, at which the participants—some 150 scientists, representing various lines of work—decided to form the American Society of Human Genetics. The two major purposes of this organization were to be the furtherance of sound research in this subject and the publication of a journal dealing with such research. The Society was officially organized at the September, 1948 meeting of the American Association for the Advancement of Science in Washington, D. C. The first meeting for the reading of papers will be held in New York City next December and those desiring to take part should write to the Secretary of the Society, Dr. Herluf H. Strandskov, Department of Zoölogy, University of Chicago.

In a sense, the establishment of this society and journal has been long overdue, since most of the basic principles of "modern" genetics, applicable to living things in general, have been known for over a third of a century. Moreover, it has long been evident that the specifically human problems of genetics constitute such an immense and complex group of fields, and require for their successful prosecution such a combination of the knowledge of specialists in the respective human subjects with a thorough working understanding of genetic principles, that societies devoted mainly to general genetics are inadequate for dealing with this material. However, an unfortunate compartmentalism has for many years hindered persons in medicine and in the other specifically human disciplines from attaining the necessary knowledge of genetics and, *mutatis mutandis*, has hindered geneticists from mastering the more special human subjects. Although this situation has prevailed for over a generation, we believe that the time is now ripe for a fertile liaison, and it is the purpose of the present society and journal to subserve it.

Included in the ranks of our present group there are many persons of genetic competence who are primarily medical men, of varied specialties, there are some genetically qualified anthropologists, psychologists and students of social sciences, and there is a good share of persons whose main field is genetics itself but who have acquired a considerable interest in and knowledge of one or more of the specifically human subjects. Our board of directors and our editorial staff have been chosen so as to represent all these groups. We hope therefore

to be able to avoid that dilettantism which has in the past characterized so many attempts to study human heredity.

II. ERRORS TO BE AVOIDED

It happens that the prolonged delay in setting up the present working association has one very fortunate aspect. This derives from the fact that, until very recent years, the subject of human heredity was buffeted about by pressure groups from the extreme political right and left, who sought to impose their social preconceptions in the form of a spurious "nature-nurture controversy", in which the methods of objective science were largely forgotten. The development of a more scientifically minded group of students of the subject has required the influence of basic genetics, working over many years. And in recent years, this sounder attitude has been reinforced by the lessons of the terrible mistakes made by the political protagonists of fascism and of communism, respectively, when they gained the power to translate their biological prejudices into action.

Reactionaries who assumed that practically all social ills were results of inferior hereditary endowment on the part of the classes and peoples having an economically lower status had been prominently represented in the old-style eugenics movement, and this movement in turn played a major role in the motivation of the earlier studies on human heredity. These eugenists usually assumed naively (1) that the characteristics manifested by the economically more advanced groups (or thought by members of those groups to be so manifested) were superior ones and those of the contrasted groups inferior, and (2) that the characteristics, whether physical or mental, manifested (or thought by biased observers to be manifested) by any person or group were in the great majority of cases valid signs of corresponding differences in the underlying genetic endowment. In these self-flattering rationalizations, the influence of environment on the supposed differences was neglected or minimized.

This kind of wishful thinking, indulged in by members of a dominant group, was long ago formulated on a racial basis by Compte de Gobineau. It flourished increasingly in the "eugenics" of such racist propagandists as Lothrop Stoddard, Madison Grant, and Fritz Lenz. Finally, blossoming out into the Nazism of Hitler, it led to such excesses as to involve itself and a considerable portion of the world in ruin. Although in this process its fallacies became widely exposed, it is by no means all dead and buried yet, but represents a continuing peril, to be vigilantly guarded against by all serious students of human genetics.

Equally irrational is the view that, after evolution had finally arrived at the stage of man, all hereditary differences became unimportant, that genetic "equality" of individuals as well as of all groups is an established fact, and that, as regards the innate basis of human mental traits at least, there are no

significant qualitative or quantitative differences which can markedly influence the nature of the developed product. Here, environment is supposed to be the practically absolute dictator.

The atrocities to which the latter kind of "retreat from reason" can lead in the hands of unscrupulous authorities have been made clear in recent months by the officially admitted liquidation of all genetics, and of much of science in related fields, within the Soviet Union and its satellite countries. Setting up in the gap thus left open the archaic doctrines of direct adaptability of the germ plasm and the inheritance of acquired characters, these would-be environmentalists have however got themselves into a self-contradictory and awkward position. For, on their view, the effect of environment, being inherited, is necessarily cumulative from generation to generation, and so the less privileged classes and peoples would after all these centuries have become innately inferior. Some proponents of the view, when questioned about the matter, have reluctantly admitted this, saying that several generations would be required to overcome this supposed inborn handicap, although, in time, better conditions of living would automatically improve the stock. The Presidium of the Academy of Sciences of the U.S.S.R., however, in an official announcement, has attempted to sidestep the embarrassing discussion by saying that "to apply biological laws to human beings is to lower them to the level of beasts." According to this escape, only social laws operate in determining human nature, at whatever level.

Such are the dangers attached to a subject which lies so close to the interests of men, and to the scene of political, economic and ideological conflicts. It then becomes the more necessary for the scientists engaged in it to dissociate themselves from those powerful currents in which reason is swayed by passion, to resist the incursion into their field of prejudice, of whatever origin, to hold fast to the hard-won results of painstaking experiments, observations and calculations, to maintain objectivity of method, independence of thought, searchingness of analysis and freedom of criticism, no matter what "authority" may thereby be challenged. Fortunately for most Western scientists there are still, in their countries, considerable opportunities for pursuing such a course. It is, however, their obligation, along with that of all other men of good will, to aid actively in that concerted effort which experience has proved to be necessary for the continued maintenance of their opportunities for intellectual integrity. But all this serves to clear the ground for their specific tasks.

III. THE RELATION BETWEEN HEREDITY AND ENVIRONMENT

Let there be no mistake about the nature of these tasks in the subject of human genetics. Consider first the "nature-nurture controversy". The developed organism is more nearly a product than a sum (though actually a group

of far more complicated functions) of the sets of factors which constitute heredity and environment. This is illustrated by the fact that, with either set of factors effectively at zero, the resultant too, the organism, becomes zero. By suitable variation of either set of factors, moreover, the product can, conceivably, be affected to a virtually unlimited extent. In this sense it is illegitimate to ask, which is more important—heredity or environment? Yet in given situations, when dealing with particular characteristics, the actually existing differences of environment may be more or may be less effective than those of heredity in altering the observed outcome. There is no general solution, for the specific results will vary enormously according to the nature of the characters, the nature and range of the environmental conditions, and of the genotypes in question. Yet these specific findings are often highly important. They can be attained not through *a-priori*-based argument, but only through observations and measurements made under suitably controlled conditions.

It is perhaps necessary to labor the point that no fallacies in genetics are more absurd than the two complementary assumptions, made by so many laymen: (1) that, because a certain ailment or other characteristic is found to be inherited, we must regard it fatalistically, and set it down as something impossible to influence by environmental means, and (2) that because a certain characteristic is found to be acquired as a result of the action of environment, it is not also subject to hereditary influences. True, there are some traits, such as eye color or blood type, which are much subject to hereditary differences and, ordinarily, very little to environmental ones, although special conditions can be found which affect even these. And there are others, represented by the acquisition of a highly infectious disease, or a given language, or the breaking of a bone, which are to a paramount degree determined from without, though even here hereditary predispositions sometimes play a role. But the great majority of respects in which organisms differ fall between these two extremes. That this is true of most characters, both "physical" and mental, in human beings has been shown clearly by comparative studies on one-egg and two-egg twins. This elegant mode of attack, which so largely compensates us for our inability to obtain pure lines of human beings, is capable of yielding far more information on these questions than it has so far. In this kind of material, moreover, there is opportunity for a certain amount of experimentation, to determine the effectiveness of particular types of changes in environment.

The ascertainment of the extent to which the ordinarily observed differences in a given character are genetically or environmentally based is only the beginning of the serious investigator's job. For, whatever the answer may be for the differences as ordinarily found in his particular population, under the circumstances there prevailing, it may be quite different for another population, and/or under other conditions. His final aim therefore should be not

merely an over-all statistical description, but an analysis of the mode of operation of each significant factor. Only this will give security to his predictions for combinations of circumstances not already met with, and will bring his conclusions to the point where they are likely to have useful applications in practice. It is true that, owing to the immense complexity of the organism, and of its conditions of life, this job is in an ultimate sense almost an endless one. Yet this does not prevent the attainment of most important and useful information along the way, as the analysis, in its interwoven genetic and developmental aspects, reaches ever deeper levels.

The above point of view, so self-evident nowadays to those initiated in genetics, was not established readily or rapidly. It involves the whole distinction between phenotype and genotype. This had its start when Weismann called attention to the continuity of the germ plasm, and its distinction from the soma. It developed further as a result of the findings of cytologists, Mendelians, mutationists, and "pure line" workers like Johanssen, showing the relative stability of the hereditary material and the independence of its transmission from ordinary environmental influences, while at the same time experimental embryologists and physiologists were demonstrating the responsiveness and adaptability of the somatic structures and processes. And as genetics and the other fundamental biological and medical sciences have developed, our view of these matters has become increasingly concrete and detailed.

IV. EARLIER HISTORY OF HUMAN GENETICS

As the foregoing account has indicated, human genetics has been extremely dependent, for the correctness and usefulness of its interpretations, and for guidance as to significant directions and methods of research, on the progress of the sciences basic to it, and more particularly upon general genetics. It must always keep a firm foothold on this base. For, important though its special problems are for mankind, most of the fundamental principles of genetics, which are as it were its tools, have first to be worked out in pilot experiments on lower, more controllable organisms.

It is true that Francis Galton attempted to found a science of heredity and variation through a statistical study of the characteristics of human parents and their offspring. Thus he set up his so-called "law of ancestral inheritance" and the "theory of regression". However, the Mendelian studies on lower forms showed how misleading these findings were, when taken as guides to what happens in the individual organism. Even though the "law" itself is in the main correct if taken descriptively, it turns out to be a complicated resultant of the action of the Mendelian processes working in large populations, in combination with the action of environmental influences on the development of the same characters, in ways which the statistical study of heredity as employed by

Galton and his gifted but too stubborn follower Karl Pearson could never by itself have revealed. Basic knowledge was not yet ripe for a science of human genetics in Galton's time.

But though a science of heredity was not thereby established, something else did emerge. For the mathematics of statistics became in the process a full fledged and highly useful set of methods, applicable to problems in economics, psychology, physics, and various other fields. In human heredity these mathematical tools are in some lines quite indispensible, when taken in conjunction with the interpretations which general genetics, based on Mendelism, affords. Through the modern refinements of its operations, that inability to control individual crosses which so hampers the drawing of exact genetic conclusions is often in considerable measure circumvented nowadays by statistical mathematics. And, in some degree, it is almost universally necessary for helping to determine just how sure a given conclusion may be, or how wide is the margin of error of a calculation, whether in genetics or elsewhere.

With the coming of Mendelism, those students of human heredity who were scientifically more progressive began interpreting the inheritance of individual traits, as shown in pedigrees, on a Mendelian basis. The foremost pioneer in this work was Davenport, who deserves especial credit because he had been trained to look at heredity from the Galtonian angle. He organized such researches on a considerable scale, while others, in Germany and England especially, followed suit, and innumerable cases were amassed and fitted into the supposedly simple Mendelian scheme.

Unfortunately, the concepts of multiple gene action on the same character, and of environmental interaction in the result, which general genetics had only begun to demonstrate, were as yet insufficiently appreciated by these early workers with human pedigrees, even though Davenport himself did adduce sound evidence for multiple gene differences in skin color. Moreover, these enthusiasts usually failed to recognize differences in the degree and quality of the condition studied, forcing it into rigid presence-and-absence categories to correspond with their oversimplified conception of the genetic and developmental basis. And in deciding its presence or absence in each individual they commonly accepted the verdict of untrained observers, no matter how technical an adequate diagnosis of some of the clinically peculiar conditions might be. Finally, their cases were often selected for conformity with the schemes they were to follow, or at least for showing numerous "positive" individuals, and the effects of this selection of material were not allowed for. All this patent forcing of the data, and, still more so, of the interpretations, led many critically minded persons to look askance at both the specific and general claims made. Even more so did the fact that these precarious conclusions were often used in support of sweeping recommendations for eugenic measures, and that many

of the studies were indeed little more than accessories, made to put forward the preconceived eugenic notions of the writers.

Quite obviously the cart had been put before the horse, to the detriment of both. It would be helpful, for those now intending to work in this field, to examine some of these early reports critically, as object lessons of what procedures to avoid. Unfortunately there is still a good deal of material of this kind published, but now it exists chiefly in scattered form, in medical and biological journals primarily devoted to other objectives than genetics.

V. TRENDS IN SOME OF THE MODERN WORK

Since the days when literature of the above type set the standard in human genetics, there has been an enormous improvement. Thus, the *Annals of Eugenics*, passing from Karl Pearson into the hands of R. A. Fisher and L. S. Penrose, has set a very high standard for work of a statistical kind in which those processes of Mendelian recombination, linkage, multiple gene action, environmental interaction and mutation frequency established by general genetics are used as the elementary operations in the computations. Likewise the gathering and interpretation of pedigrees dealing with particular traits has been handled in a truly scientific manner in such work as that of the great Medicogenetical Institute which, with its 200 or more participating physicians, flourished under Levit in Moscow from 1929 to 1936, when it was liquidated. Much good work of a similar nature has been carried out, though with more modestly organized plans, in this country, the Scandinavian countries, Great Britain, Switzerland and Holland, as well as (if we make the right selections) in Germany and Japan.

In the modern work with pedigrees, the recognition of grades of "expressivity" and of "penetrance" of a gene (to use the terms of Timoféef, first applied in human heredity by Oscar Vogt) and of the "conditional" as well as vacillating nature of dominance (Levit) has helped considerably. So has the finding of special techniques for recognizing the presence of given genes when their conspicuous effect is absent, as in Mohr's X-ray identification of hidden carriers of brachyphalangy, Levit's blood-sugar determinations of unexpressed diabetics, Valentine and Neel's diagnosis of heterozygous thalassemics, the use of "brain waves" for spotting latent epileptics, Vogt and Patzig's finding of nervous symptoms disclosing subliminal cases of hereditary chorea, etc. This approach can be vastly extended, to great advantage for both medical diagnosis and prophylaxis. It is evident that success in the working out of such matters requires, on the one hand, high genetic competence, both for the provisional interpretations of pedigrees that guide the choice of individuals to be examined, and for the later assessments of results, and, on the other hand, detailed knowledge of the condition in question and of the techniques that

might be used in examining it. This means either a combination of the two disciplines in the same person, or effective collaboration between an up-to-date geneticist and an investigator who has made a special study of the particular field in question.

VI. "PHYSIOLOGICAL GENETICS" IN MAN

Surely the most striking illustration of the value of advanced techniques in the tracking down of genes is provided by the findings on the inheritance of antigens, as seen especially in the Rh and other series found in human blood. Although such work is still in its early stages (if we consider the much greater multiplicity of antigenic differences already demonstrated in the blood of cattle) it has already done more than perhaps all other work in human heredity combined to bring home to medical men the reality of the processes of inheritance dealt with by geneticists, and their relevance to problems of medical diagnosis, therapeutics and prophylaxis. One of the chief aims of human genetics must be to get the recognition of as many genes as possible on to a similarly definite basis.

The rapid rise in our knowledge of proteins and other biological substances, and of their interactions, should open many rich veins of genetic investigation to parallel that of the blood antigens. At the same time, as has been so well demonstrated in the studies on molds and bacteria, the intensive biochemical investigation of hereditary deviants is of great aid, reciprocally, in advancng our knowledge of the biochemical materials and reactions concerned themselves. As illustrations of such leads in our human material, we may mention such hereditary abnormalities of metabolism as are found in alcaptonuria and phenylpyruvic amentia, which surely represent but an insignificant fraction of the hundreds of chemical variants that must exist in man.

But it is not only on a biochemical level that the exact study of mutants, in comparison with the standard form, throws light on the processes occurring in the organism. The same is true in the study of physiological and pathological reactions in general, and in the study of development, including the processes of regeneration and of aging. Each mutant which distinctly affects development or physiology represents a research problem in itself, which is likely to be as profitable, and often much more so, for the elucidation of normal functioning, than a laboratory experiment in which the given part or character is investigated by means of surgery or medication. In fact, the unravelling of the whole great complex of biochemical, developmental, and physiological processes which constitute the organism must in time proceed more and more through the study of these very delicate experiments which nature provides ready-made for us, when presenting us with changes in the individual genes lying at the basis of the formation and of the workings of all somatic parts. And as in other fields

it cannot be otherwise in this, that increasing knowledge will carry in its train increasing possibilities of control.

Man is so closely related to the other vertebrates, particularly the mammals, that much of this genetic dissection of development and physiology can be carried out most profitably through pilot work on laboratory forms. Excellent examples are the intensive studies of Landauer on "rumpless" fowl, of Dunn and his associates on caudal abnormalities of mice, of Grüneberg and of Bonnevie on the developmental physiology of changes in the circulatory system of mice. It is likely that many results of this kind carry their lessons with regard to corresponding processes in humans and will later be found to be represented by homologous human cases. It is therefore worthwhile, on occasion, for a journal of this kind to consider them. On the other hand, men are examined intensively in so much greater numbers than any animal, that the human material itself will often present the pilot findings, which can later be followed out in more controlled fashion in animals.

VII. QUANTITATIVE INHERITANCE

The genes referred to in most of the above discussion are such as to give sharply recognizable differences. It should however be remembered that most of the gene differences prevalent in populations, distinguishing individuals phenotypically, only affect, at least as the end product of their action, the quantity of some character or characters. Usually the effect is also modified by the action of environmental conditions and of an undetermined but often large number of other, coacting gene differences, not readily distinguishable from them. We are thereby confronted with problems of multiple gene inheritance. For their study, in the absence of definitive signs of the individual genes, an approach combining the principles of Mendelian inheritance with the methods of statistics adapted to the latter are necessary. Through these means, although the genetic composition of the individuals themselves remains largely undetermined, nevertheless considerable progress can be made towards predicting in a general way the probable results to be expected from given types of crosses.

One of the objectives in such work must be the obtaining of evidence concerning the relative frequencies, in the population, of gene differences having different degrees of effect on the given character—i.e., a frequency-magnitude of effect distribution. Other objectives are to gain evidence as to degrees and direction of dominance shown by the gene differences of different magnitude, and as to the extent to which the effects may be treated as simply (logarithmically) cumulative or, contrariwise, as embodying more specialized types of interaction with each other and with environmental effects. Nor can the answers for one type of character, such as stature, or for one population, such as

West Europeans, be carried over without verification to another character, such as head-shape, or to another population, such as Eskimos.

Now it might be thought that in prosecuting such studies we are passing over from characters of medical interest to those which concern more purely the physical anthropologist. However, there is no fundamental distinction between gene differences of the more extreme and usually rarer kind and those of the less extreme and usually commoner kind; they grade imperceptibly into each other. Although the primary gene effect is probably in the vast majority of cases a qualitative chemical one, studies on lower forms show that it usually expresses itself through its quantitative influence upon some chemical process concerned with development or physiology, even when the final outcome again appears as a qualitative difference. And so the cumulative action of a number of minor differences that happen to work in the same direction may be as great as, and very similar to, the action of one "large mutation". To know how often to expect effects of different degrees, then, from given types of matings, we should know the frequency distribution of the gene differences of different magnitudes. *Vice versa*, the latter may to a certain extent be estimated from data concerning the former. But as yet there has been little attack upon these difficult problems. Their very formulation shows us, however, that there is no sharp category of "abnormal" versus "normal" variants. And medicine and even psychology, along with anthropology, will increasingly have to take the so-called "normal variations" into consideration in their judgments concerning diagnosis, prophylaxis and treatment.

VIII. GENETICS IN RELATION TO MENTAL PROCESSES

A few additional words are perhaps called for concerning the role of human genetics in relation to fields dealing with mental processes. Here more than anywhere else strong rancor was aroused by the sharp cleavage into hereditarians and environmentalists, and there are still many vehement proponents of these opposite extremes to be found, chiefly among persons not well grounded in modern genetics. It is germane in this connection to remind ourselves that the brain is an organ constructed for the achievement of maximum plasticity in response,[1] and that its reactions are therefore influenced in a far more thoroughgoing way by environmental differences than are those of any other organ. When it is recalled, in addition, that a vast store of environmental influences is handed down in families, and in whole groups, through unconscious as well as overt tradition, and through the transmission of the material means of existence, and, further, that all these factors are themselves subject to the most profound and marked continuing differences, it is seen how ultra-cautious the

[1] Paraphrased from a passage (p. 433) in the author's study of a case of identical twins reared apart (Muller, 1925).

investigator must be before ascribing any apparently inherited behavioral characteristics to the genes. In fact, these considerations are enough to make it quite illegitimate to make any deductions regarding genetic differences for mental traits, on the basis of comparisons between individuals or groups whose cultural or material background have been consistently different.

Despite the above stricture, however, innately determined features of the brain are of the utmost complexity and they must, like the minutiae of all other organs, be subject to genetic variations of innumerable kinds. These variations are bound to affect brain functioning in manifold ways not yet understood, contrary to the assumptions of those who claim that the genetic variations which can significantly influence behavior are confined to alterations in the production of hormones and in the form and functioning of other parts of the body than the brain itself. It is biologically certain then that there must be many important individual differences in behavior caused by genetic changes which directly affect the central nervous system. The discovery of these differences, the unravelling of their genetic bases, and of the manner in which they interact with influences emanating from the environment (using this term in the broadest sense, to include also the social environment) constitutes a tremendous field of research for psychologists, psychiatrists and all concerned with mental processes.

The disentangling of genetic from environmental effects on behavior, or at least the comparison of their nature and magnitude under given conditions, is not, as might at first sight seem to be the case, an impossible task. For some very valuable data along these lines have already been obtained, through those special techniques which provide us with relatively constant environment while the genotype varies and, conversely, with a relativcly constant genotype while the environment varies. Included among such techniques are, *par excellence*, comparisons of the amounts of difference between the members of one-egg and of two-egg pairs of twins. This attack has been broadened by the inclusion of cases of one-egg twins whose members were reared apart, or purposely subjected to different treatments. Further light on the subject has been obtained by the parallel investigation of ordinary sibs, of foster children, and of persons of different genetic background brought up in the same institution. All these results agree in ascribing very important roles to *both* the hereditary and environmental factors involved, in the case of the great majority of the mental traits studied. These are, however, but token investigations of the kind, compared with what yet remains to be done. Furthermore, since they prove that many of the more extreme mental differences between members of the same family must be largely genetic in their basis, it becomes justifiable to some extent to use the pedigree method of investigation also, although not so indiscriminately and incautiously as in most of the earlier work. And it goes

without saying that, in such studies, the precautions and skills of the professional psychologist or psychiatrist must be brought to bear.

IX. GENE FREQUENCY STUDIES

Passing beyond the more usual interests of the physician or psychologist in the individual man we come to the problems of the underlying biological basis of the health, vigor, capacities and properties of varied kinds genetically inherent in entire interbreeding groups of people, of the factors that brought them to their present state, and of those that are working to alter them still further.

In these studies on the genetics of populations it is of course the more definitely recognizable genes which usually serve as the more useful indicators. The work on antigen frequencies just opening up is an illustration of investigations of this type that promise to be most informative for the physical anthropologist in tracing the historical interconnections and migrations of peoples, and the conclusions on these matters will in turn be highly important for the cultural anthropologist. Of greater general biological as well as medical interest, however, will be data on the frequencies of lethal genes and of those producing various grades of detrimental effect, and on the amount of concordance in the nature of these genes in different populations.

These frequencies are known, from considerations of general genetics, to be in the main, for a given mutation rate, reflections of the nature of the breeding system: such as the amount of inbreeding, the kind of exogamy or endogamy practiced, the amount of migration, the population size, the extent of subdivision into smaller populations and their size and degree of isolation. The rigor and type of selection presents further variables of great importance here. Theoretically, if we had quantitative values for these factors and also knew the basic mutation rates of the genes concerned, we could calculate the results to be expected. Conversely, having the end results and having general values for all but one of the above sets of factors—for instance, the mutation rate—we could then arrive at an approximate estimate of the latter. Such solutions would in turn enable us to forecast how the values would change in response to alterations in the system of breeding or of selection. And, in time, actual evolutionary implications would emerge.

As it is the mutation rate which furnishes the primary pressure for the apparition of all the observed "abnormalities" their numbers will, other things being constant, be directly proportional to this mutation rate. It may, in most cases, be taken as a fixed base of reference, and a knowledge of it is one of the prime desiderata for our calculations of populational composition. Fortunately, a good deal of significant information can be obtained about mutation rates without use of the elaborate breeding methods employed in experimental organisms. For example, the simple relation that, for dominant genes which are not lethal to the fetus but render their bearers incapable of reproduction,

the frequency of individuals manifesting the disorder is exactly double the mutation frequency, allows us to derive the mutation frequency of all of these genes which can be definitely recognized. This has been done, with consistent results, in some cases approaching these conditions. However, we must make the qualification that there has as yet been no proof that just one gene locus was involved in the case of any of these abnormalities, rather than a group of scattered loci whose mutations produced similar phenotypic effects, as in the case of the *minute bristle* condition in Drosophila.

Similar considerations apply for any gene of which a fairly good estimate of the reproductive capacity of the individual exhibiting it may be made, as in the case of highly detrimental conditions like hemophilia. For in such cases, the amount of reappearance of the mutant in the population, caused by its own reproduction, can be allowed for, and then it is again possible to determine the mutation frequency of the gene from the frequency with which the given character is present in the population. It is thus evident that, both for mutation rate studies in themselves and, through them, for conclusions regarding population genetics, it is imperative to have more exact data on the actually existing frequencies of the various ascertainable hereditary ailments. At the same time, estimates should be sought of the amount of detriment which these ailments entail in reproduction.

The influence on the mutation rate of various factors, such as radiation, aging, or chemicals, is hardly a subject that can be investigated profitably in human material. It is a matter of great ultimate importance for human beings however, and so it is necessary, in the interests of our knowledge of human genetic processes, to conduct such studies on related, i.e., mammalian material. Such material must also be used for obtaining frequency distributions of the relative numbers of mutations of different types, since in man the types of mutations suitable for mutation frequency studies are as we have seen so much more limited. If then our results with different experimental organisms turn out to be in satisfactory agreement, we may fairly infer that a similar situation exists in man, and base our calculations accordingly. Of course there is no reason, even now, to doubt that such generally acting mutagens as high-energy radiation and mustard gas are effective in man, and, in the case of radiation, that the effect is proportional to dose. The question however is, what is the order of magnitude of the effect for a given dose. This we must know, before we can forecast quantitatively to just what extent the techniques that are being used will be reflected in the well-being of future generations.

X. THE MAPPING OF THE HUMAN GERM PLASM

So-called "formal genetics", of the type carried on extensively on Drosophila and maize in the early days—the making of maps of the chrososomes, would seem an almost utopian objective for human material. Yet a fair number of

loci have already been approximately mapped along the sex chromosomes of man. And, with special statistical aids applicable to the data from small families in which the original gene arrangements were unknown, probable cases of linkage, involving crossing-over, have been discovered in other chromosomes. The recent findings of so many identifiable hereditary antigens will greatly facilitate such work and it is not unlikely that, if the number of definitely recognizable characters increases rapidly, there will, even in our generation, be a real opportunity for the construction of genetic maps. In these, the landmarks formed by the good "marker" genes should in turn facilitate the finding and locating of genes that would otherwise be harder to follow.

There is probably little of immediate practical value soon to be derived from such studies. However, it should be beneath the dignity of man to be content to remain forever ignorant of such basic facts of his own structure. Moreover, as more and more information of this sort is gained, it should eventually be of use in allowing us to follow the transmission of chromosomes and chromosome parts and so even to deduce, to some extent, the pathways of inheritance of those genes whose effects, for whatever reason, could not individually have been spotted by themselves. Thus, if a recessive lethal had been known to be closely linked with a given antigen, and the antigen was found to be received by a given offspring, it could be taken as highly probable that the lethal had been received as well.[2]

With chromosome mapping there also goes the possibility of studying such genetically observable aspects of chromosome behavior as crossing over, nondisjunction and structural change. These too must some day become objects of genetic research, even in human beings. Long before such genetic data can become available, however, there is bound to be a great increase in cytological knowledge, and it is unnecessary at this stage of genetics to have to explain in what numerous ways cytology can aid in interpreting the results of breeding. From the work of Winiwarter and of Painter on human chromosomes as seen under the microscope to the recent work of Schultz & St. Lawrence (1949) is a long stride, and this achievement gives promise of providing cytological maps long before the corresponding genetic ones are available. Moreover, we must not forget that, through still newer techniques of observation, the resolution may be still further increased. And, with the use of tissue culture methods, even experimental cytology of various kinds becomes possible with human material, as was demonstrated by Shiwago in his *in vitro* studies of the chromosomes in human epidermal cells and leucocytes.

[2] The eventual applicability of this type of inference in human inheritance was pointed out by Altenburg and the author (1920) in their account of the inheritance of *truncate wing* in Drosophila—the first case in which the methods of "markers", as it is now called, was used in the analysis of a multiple gene situation (see pp. 51–52 and 59 of that article).

XI. POLICIES OF THIS JOURNAL

It is hoped that the above very rambling discussion will at least show how very multitudinous and far reaching the subject of human genetics is, and how requisite it is that the work in it be carried out by persons highly proficient in the particular field concerned. They should at the same time be well versed in general genetics, in its modern form, or, failing this, work in close collaboration with persons who are primarily geneticists. Here we are faced with the deplorable situation that, with relatively few exceptions, genetics is neither a required subject for medical men, psychologists, anthropologists nor students of the social sciences, nor even taught in medical schools themselves. For this reason this great world of problems, so intriguing yet so difficult and so little explored, must for the present be left to a body of trained personnel which is quite inadequate in numbers. If however they emphasize quality rather than quantity of work in their attack, their results will in time convince the less initiated of the importance and richness of the subject in relation to all branches of medicine and of human biology.

The recognition consequent upon these advances will gradually lead to measures for the better training of the younger generation, and as a result the cadres involved, and the volume of their work, will in time become greatly augmented. Thus we may confidently look forward to a day, not many decades hence, when, in place of one journal to cover the whole vast group of subjects herein comprised, there will be a considerable group of periodicals, each devoted to its own special field. Until that day comes, however, the present journal must remain so diffuse in its range that only a portion of its articles will be intelligible to any individual reader. If we insisted on a general intelligibility, we should have to sacrifice that technical quality and significance for which we stand to the interests of a shallow popularization which could best be carried on by other organs. At the same time, however, it should be the duty of the journal also to include some more general articles, which interpret one field of work for the benefit of specialists in other fields, and to make even its more technical articles as generally understandable as is consistent with a high level of scientific contributions.

For those insufficiently versed in general genetics who would read this journal it would not be feasible for our authors continually to go out of their way to explain established principles and operations. They should avoid, however, the older-style treatments which, instead of stressing methods, precautions and general principles, attempt to present compendia of the voluminous material piled up by uncritical pedigree collectors. Similarly, in so far as the more specialized medical and other human fields are involved, we must assume a general familiarity with any such subject on the part of the reader of any article dealing with it. We would remind those who have hitherto regarded genetics as "too

technical" that there are various excellent introductory text books of general genetics, such as those of Altenburg (1946), Sinnott and Dunn (1939), and Snyder (1946), to mention but three, a reading of any one of which should be sufficient to put them abreast of the genetic terms and concepts used in the pages to follow. If they prefer, they could turn instead, or in addition, to some introductory volumes dealing more specifically with human heredity, such as those provided by Roberts (1940) or by Crew (1947).

The question will be asked, what attitude will our society and our journal take towards the presentation of eugenic topics? We must answer, first, that our primary purpose is research in human genetics, the laying of a firm basis of methodology and of factual knowledge. This knowledge is as much an end in itself as any other knowledge—or even more so, if we admit that "the proper study of mankind is man".

However, we recognize also that this knowledge *may* and—if mankind continues to advance—*will* eventually be put to use, and this realization certainly acts to strengthen our motivations in the prosecution of these studies. Now, one series of uses of the knowledge (also sufficient as an end in itself), is the far greater degree of control over our present somatic constitutions and reactions, through improvements in medical methods and in general ways of life, which must follow in the train of such knowledge. This bettered control would be an inevitable consequence, first, of that deeper insight into normal mechanisms which is to be gained through "physiological genetics" (including here also its psychological side), and second, of the increased ability to detect detrimental deviations while they are still latent, to guard against their development, and to treat them if they have occurred. Conversely, latent qualities of a desirable nature could be better spotted and made use of. In all these way genetics comes to the service of organisms without interfering with the genetic bases underlying them.

All the above is not to say that these are the only ways in which genetics can be applied. There remains, not least, the question of the guidance of reproduction away from genetically less favorable and in the direction of more favorable paths, in other words, the question of eugenics. As we have pointed out above, this whole subject has fallen into disrepute because it has been so perverted by unscientific propagandists and cranks, with hastily conceived remedies which they desired to foist upon the community as substitutes for social measures with which they did not agree. We do not wish this kind of eugenics. Neither would it serve the advancement of human genetics to have our society and journal become organs of agitation. It is to the detriment of research for it to have to use the same channels as those for propaganda, even if that propaganda is of a desirable kind.

At the same time, we must be careful not to be panicked into throwing away the wheat with the chaff. It is the present writer's considered opinion that eugenics, in the better sense of the term, "the social direction of human

evolution," is a most profound and important subject and that it will in due time be worked on seriously, not in a spirit of ill-considered partisanship and prejudice, but in one of scientific objectivity combined with social consciousness. Moreover, the effective recognition of either especially detrimental or especially valuable genes is by no means so impossible as some objectors have claimed—if it were, no natural or artificial selection could ever have succeeded. But the heat and the misunderstandings of present political controversy, and the prejudices rampant in all existing societies, make very bad soil for the development of sound eugenic policies at the present time.

For the above reason we can as scientists best pave the way for a proper approach to such applications by devoting our main present energies to the building up of an ever more thorough understanding of the genetic basis of mankind, of its transmission, its variations, its modes of expression when in combination with different environmental factors, and the changes which it undergoes in populations that are subject to different systems of breeding, selective conditions, mutagenic influences, etc. As these topics are dealt with, it should not be held amiss if the investigator utilizes the occasion to draw lessons concerning the effect of this or that situation on the human genotype, and concerning possible means of avoiding ill effects or gaining advantages for it. In this way, gradually, the basis may be laid for a calmer, more detatched and scientific consideration of these topics than has heretofore been possible.

It is to be hoped that, by the time this ripening has occurred, the racial and class biases so rampant in most societies today will in considerable measure have been smoothed out. This will allow attention in the subject of human heredity to be drawn away from those conspicuous but superficial group differences which for most people now loom so important, and facilitate the more intensive study of the genetic differences within populations. For present information gives good ground for the conclusion that these individual differences, on the whole, concern far more important characteristics, and are, on the average, of much greater magnitude, than the differences between the averages of present racial or economic groups. This realization should make possible a far more unbiased treatment of the whole matter, one in which unthinking group pressures have been reduced to a minimum. Meanwhile, let us bend our main efforts to the increase of basic knowledge.

Whatever may be the reader's opinions on the subject of eugenics, we invite him to participate in the building up of this journal, if only he is willing and able to join in the development of the factual and methodological basis of human genetic study. Medicine in all its branches is overflowing with genetic problems open to investigation, and many of them can be tackled in the course of the day's work, without the practitioner going far out of his way. Ophthalmology, pediatrics, orthopedics, immunology, dermatology, neurology—what field concerned with medicine or, for that matter, with the so-called normal man, can be named in which interesting and important deviations of a familial nature

are not to be found? These must be studied, however, not with the slip-shod casualness characteristic of the earlier reports, if they are to serve as stepping stones to a more integrated knowledge of the foundations of the organism. The investigations should be carried out with the aid of the best awareness of modern genetic principles and possibilities, and with the best statistical tools that are available. In this way we will come at last to know ourselves.

Although we hope our own *Journal* will serve as a center in North America for the bringing together of such studies, we believe it to be desirable for those American journals which from time to time carry articles on human genetics to continue to do so. The cleavage of subjects should not be absolute, and it is well for those whose center of interest is somewhat different from ours to have these opportunities of remaining aware of our own field. The numerous scattered articles of more or less genetic interest which appear in medical journals are on the whole well placed there. They will make it easier for the specialized genetic journals of the respective fields to take shape when the time is ripe. The journals dealing with general and experimental genetics, and more particularly *Genetics* and the *Journal of Heredity*, which have published many valuable papers on human material, will, it is hoped, continue to invite such papers. We also wish to acknowledge our appreciation of the important work on human genetics published abroad in such periodicals as the *Annals of Eugenics*, *Archiv der Julius Klaus-Stiftung*, *Genetica*, *Hereditas*, *Heredity*, and the *Journal of Genetics*. Most particularly we send our greetings to our older brother, *Acta Genetica et Statistica Medica*, whose first number appeared a year ago. This journal is under the able editorship of three leading geneticists who are at the same time medical men, Gunnar Dahlberg, Head of the State Institute for Human Genetics at Uppsala, editor-in-chief, Tage Kemp, Director of the University Institute of Human Genetics at Copenhagen, and Otto L. Mohr, Rector of Oslo University. It is devoted to the same purpose as ours, and should be followed with especial interest by our readers.

H. J. MULLER, *President*
American Society of Human Genetics

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The Detection of the Genetic Carriers of Hereditary Disease[1]

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I

In selecting a topic suitable for consideration by the American Society of Human Genetics on the occasion of this, the organization's first meeting, I have been guided in large part by the feeling that the very broad and general aspects of the study of heredity in man have for the present been sufficiently discussed in numerous articles and addresses, and that we might more profitably spend our time today delving into some specific problem in our field of common interest. For while the objectives of the study of human heredity have been frequently and ably stated, the specific approaches whereby these objectives may be attained are only now in process of definition, and detailed and exact knowledge of the genetics of man is still conspicuously wanting. In the past, the disparity between the broad objectives and the paucity of knowledge at hand for their attainment has had some unfortunate repercussions. Repetition of any of these errors now, at a time when there appears to be a rather general increase of interest in this country in human heredity, would be unfortunate. It is partly to stress this need for emphasis on exact knowledge in a field which so lends itself to generalities that I have chosen a rather specific topic, although one which directly or indirectly impinges on the interests of all the various aspects of human genetics represented here. This is the problem of the detection of the genetic carriers of inherited disease.

Considered from the standpoint of phenotype, two classes of people transmit hereditary disease to their children, namely, those who actually exhibit the clinical picture of the disease, and those who, while ostensibly unaffected, nevertheless include among their genetic complement genes for the disease in question. The term carrier has been applied to these superficially normal persons who transmit disease in perhaps a less spectacular but certainly more irrevocable fashion than Typhoid Mary herself, the innocent but infamous typhoid vector with whose name the term carrier is so vividly linked. The term disease is here used in a rather loose fashion to indicate any departure from normality capable of impairing the proper functioning of the individual.

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Genetic carriers may be roughly divided into two types: those who will never in their lifetimes develop the disease which they transmit, and those who may at some date subsequent to the original examination be characterized by the typical signs and symptoms of the disorder in question. The first group includes, for example, persons heterozygous for a nominally recessive gene such as that responsible for albinism, whereas the second group includes, for example, persons heterozygous for a dominant trait which is not usually apparent in youth or early adulthood, such as Huntington's chorea. It should be pointed out that in some instances it will be difficult to make a formal distinction between a carrier and an individual who shows only one of the manifestations of a pleiotropic gene.

The theoretical significance and paramount importance of being able to detect these carriers have been apparent to students of human heredity for many years. Two methodological approaches have seemed appropriate. One of these has entailed attempts to establish a genetic linkage between the locus responsible for some undesirable pathological trait and a nearby locus with nearly neutral biological effects that can be readily recognized at an early age and with a high degree of ease and accuracy, the argument being that from a study of linkage relationships within a particular family, i.e., whether the factors in question were in the coupling or repulsion phase, it should be possible to predict which members of a family might be expected to transmit a disease, or develop it in later life. The genes responsible for the A-B-O or M-N blood types in many respects approximate the ideal in genetic markers. This approach is of course closely bound up with the development of maps of the human chromosomes. The other approach has consisted of studies of the superficially normal relatives of a person afflicted with hereditary disease in an attempt to discover either in those persons who as judged by progeny tests must be carriers, or in those relatives who have a high probability of being carriers, some slight but definite stigma which will make possible the recognition of similar individuals in other kindreds or in the general population. It is the purpose of the present review to evaluate briefly the progress which has been made to date by these two approaches, to consider the limitations of each method, and to point out how those with various special interests in the field of human heredity are affected by developments in this research area.

II

We shall consider first the status of attempts to detect carriers by clinical studies, as distinguished from linkage studies. Time does not permit an extensive résumé of this topic, which has already been treated in some detail elsewhere (Neel, 1947). With your permission I shall concentrate today on certain

examples with which we or those associated with us at the Heredity Clinic of the University of Michigan have had first hand acquaintance.

Cooley's anemia (Cooley & Lee, 1925) or *thalassemia major* (Whipple & Bradford, 1936; Valentine & Neel, 1944) is a severe, chronic, progressive anemia usually terminating fatally in childhood, and confined almost exclusively to the so-called Mediteranean peoples—Italians, Greeks, Cypriots, Turks, etc.,—and their descendants. Despite its ethnological predilections, the disease was first described by a Detroit pediatrician, and Americans have been most active in the study of the condition. The manner in which important developments relating to this disease proceeded more or less independently in the United States and in Italy during the war years is another fascinating example of scientific parallelism. In this country in 1940 and 1941, some fifteen years after thalassemia major was first clearly differentiated as a clinical entity, three groups of investigators independently described a hematological disorder which had many points in common with thalassemia major but was for the most part characterized by only a very mild anemia which appeared to be completely asymptomatic (Wintrobe *et al.*, 1940; Dameshek, 1940; Strauss *et al.*, 1941). In retrospect, earlier but less clearly defined reports of this condition can be recognized in the literature (Spodaro & Forkner, 1933, *cf.* Strauss & Daland, 1948; Stephens & Tatelbaum, 1934, *cf.* Valentine & Neel, 1944). It was soon recognized that this second disorder tended to occur in the same families in which thalassemia major was present (Smith, 1942; Wintrobe, 1942; Dameshek, 1943). The systematic study of the two conditions resulted in data conforming after statistical analysis with the hypothesis that here was a homozygous-heterozygous relationship, with the mild condition, to which the term *thalassemia minor* was applied, representing the heterozygote, and the severe disorder corresponding to the homozygote (Dameshek, 1943; Valentine & Neel, 1944; Neel & Valentine, 1947). Thus, in conformity with genetic hypothesis, both the parents of children with thalassemia major have, with but a few dubious exceptions, shown thalassemia minor. Among the offspring of such parents there is a satisfactory approximation to a 1:2:1 ratio. Where only one parent shows thalassemia minor, there is a ratio of one normal: one affected among the children, and vice versa, where a child has thalassemia minor, at least one parent is found to be similarly affected.

Since 1925, the same year thalassemia major was recognized in this country, Italian authors have been writing of "itteri emolitici a resistenze globulari aumenti" (Rietti, 1925; Greppi, 1928), also referred to more recently as "anemia microcitica costituzionale" (Silvestroni, 1944; Silvestroni & Bianco 1945). Both Italian and Greek investigators observed the association with thalassemia major of certain abnormal hematological findings in other members of the family (Angelini, 1937; Caminopetros, 1937). When the first American

reports of thalassemia minor appeared in 1940, pointing out the similarity of this condition to what was then known as Cooley's anemia (Wintrobe *et al.*, 1940; Dameshek, 1941), Italian investigators were quick to recognize that the above mentioned condition in their literature was probably the same (Chini & Perosa, 1941). Apparently independently of the further American work and of one another, several Italian investigators then reached conclusions identical with those stated above concerning the genetic relation between the mild and severe anemias (Gatto, 1942; Chini, 1946; Silvestroni & Bianco, 1946; Silvestroni, 1947).

In conformity with our definition of terms above, individuals with thalassemia minor may be recognized as the genetic carriers of thalassemia major. The accurate designation of these carriers depends not on one but on several criteria, as follows:

(1) *the appearance of certain abnormal erythrocyte types in a stained blood smear.* There are two morphological aberrations of the erythrocytes which tend to characterize these people, namely, oval red blood cells, and so-called target-cells, with the proportions of these types varying from person to person.

(2) *a decreased cell size.* Characteristically, the number of erythrocytes is normal or even increased, whereas the hemoglobin and volume of the packed red cells is decreased. From this it follows that the erythrocytes are on the average smaller than normal (Valentine & Neel, 1948).

(3) *the fragility of the erythrocytes as measured by resistance to hypotonic saline solutions.* Cell fragility is decreased in thalassemia.

(4) *lack of evidence of iron deficiency, chronic blood loss, or other disease which might produce a hematological picture comparable to that of thalassemia minor.*

(5) *failure to respond to any known therapy.*

(6) *a familial incidence of a similar blood picture.*

It will be apparent that no one of these criteria is diagnostic. In the absence of family studies, utilizing all the other criteria, diagnosis is about 90–95% accurate. With the added evidence of a familial incidence of a similar blood picture, one can recognize these carriers with almost 100% accuracy.

As pointed out above, thalassemia major occurs almost exclusively among the Mediterranean peoples. Its frequency at birth in persons of Southern Italian extraction residing in this country has been placed at 1:2400 (Neel & Valentine, 1945); the frequency of thalassemia minor has been calculated from this to be approximately 4%, and this order of magnitude was confirmed by a small-scale survey (Neel & Valentine, 1947). Italian estimates of the frequency of thalassemia minor, based on direct surveys of four cities in north central Italy, are: Ferrara, 11.8%; Rovigo, 11.3%; Ravenna, 3.7%; and Bologna, 0.8% (Silvestroni & Bianco, 1946, 1947). In view of the proximity of these four cities, the differences between them are

striking. Presumably the incidence of the carrier state is equally high in other Mediterranean peoples. The possible significance to this part of the world of the recognition of the condition is obvious.

Gout is a metabolic disorder characterized by an elevation of blood uric acid levels, accompanied by acute and recurring attacks of painful arthritis, deposits of sodium urate crystals in articular, periarticular, and subcutaneous tissues, and, in the later stages, associated vascular and renal disease. About 90% of affected persons are males. A large literature attests to the hereditary nature of the disease (review in Neel, 1947). Because of the erratic appearance of the condition in succeeding generations, the accepted hypothesis has been that it was due to a dominant factor with irregular expression (Ebstein, 1906, quoted from Baur, Fischer, & Lenz, 1931; Garrod, 1931). It has been recognized since 1915 that the near relatives of patients with gout may in the absence of any clinical symptoms nevertheless show elevated blood uric acid levels Folin & Dennis, 1915; Jacobson, 1938; Talbott, 1940; Smith & Freyberg, 1942; Stecher & Hersh, 1944). Recently this question, of the occurrence of hyperuricemia in the relatives of gouty patients, has been subjected to an exhaustive and significant analysis (Smyth, Cotterman, & Freyberg, 1948), to which I should like to refer at some length.

Systematic investigation of 87 relatives of gouty patients revealed that male relatives averaged higher uric acid levels than females. In both sexes there was a definite bimodality in the distribution of blood uric acid levels. In males the first mode fell at 4.0–4.5 mgm.% with the second mode at approximately 7.0–8.0 mgm.%. In the females the first mode was at 3.5–4.0 mgm. %, and the second at 5.5–6.0 mgm.%. In both sexes the first mode corresponds well with accepted normal values, normal males averaging about 0.5 mgm.% higher than females. (Okey & Erikson, 1926; Jacobson, 1938; Brøchner-Mortensen, 1937; Berglund & Frisk, 1935). The proportion of individuals falling under the second hump of the curve appears to be the same in both sexes. If we assume that this bimodality is due to genetic dimorphism within the several families studied, and that in both males and females the genetic basis of hyperuricemia is the same, then it follows that here is an example of sex-influenced heredity. Hyperuricemia must be defined differently in the two sexes.

The distribution of hyperuricemia within the families studied followed a very definite pattern. In every single case where both parents of a gouty person were available for study, at least one of them was hyperuricemic. Hyperuricemia was also present in approximately half the siblings of gouty individuals. It follows from this that the hyperuricemic trait is transmitted in a very regular fashion, as if due to an autosomal dominant factor. Only a fraction of the individuals with the trait, about 10%, actually exhibit clinical gout.

From these genetic studies there emerges for the first time a broad hint concerning the answer to a clinical question that is at least 2,000 years old: why is gout more common in males than in females? The geneticist would be inclined to surmise that gout results in either sex whenever a certain mean uric acid level, as yet undefined, is exceeded for a certain mean period of time, also as yet undefined. Gout is more common in males simply because not only do males normally have higher uric acid levels than females but the genetic factor resulting in hyperuricemia is more strongly expressed in males than in females, with the result that many more males than females exceed the hypothetical border line separating the gouty from the non-gouty.

Hyperuricemic individuals may very properly be referred to as the genetic carriers of gout. When other causes of hyperuricemia have been ruled out, they may be diagnosed with a high degree of accuracy by the combination of genetic and biochemical studies. However, hyperuricemia has only rarely been observed in males below 20 years of age, a fact which limits the age groups within which diagnosis is possible. Further, it has not yet been established whether in these carriers uric acid levels vary from time to time in the same fashion that they do in persons with clinical gout.

The incidence of clinical gout has been estimated to be 88 per 100,000, and the frequency of carriers to be at least ten or possibly twenty times as great, or 0.9–1.8%. Here again we are dealing with a trait with a very measurable incidence.

Retinitis pigmentosa is a chronic and progressive disease of the eye characterized by atrophy and pigmentary infiltration of the retina. Affected individuals experience a concentric contraction of the field of vision, with diminution in visual acuity, which may terminate in blindness. Night blindness is frequently present from an early stage. In no other ocular disease is the rôle of heredity more apparent. Pedigrees of dominant and recessive autosomal inheritance, and recessive sex-linked inheritance have been described. The latter type is the least common. The possibility of dominant and recessive partial sex-linkage has also been raised (Haldane, 1936). Although the clinical manifestations and natural history of the disease are quite variable, within any one pedigree there tends to be a constancy of type. In addition, there are recognized a number of conditions, often hereditary, with many similarities to retinitis pigmentosa: retinitis pigmentosa sine pigmento, retinitis punctata albescens, atrophia gyrata choroideae et retinae, chorioderemia, and hemeralopia. The entire group, including retinitis pigmentosa, can be encompassed by the non-committal term "choroidoretinal degeneration".

In recent years it has become apparent that in the "recessive" sex-linked pedigrees of choroidoretinal degeneration, the heterozygous females may show changes from which they can be identified with varying degrees of

accuracy. In one pedigree of sex-linked retinitis pigmentosa in which the affected males were also quite myopic, the females who as judged by progeny tests must have been carriers were also myopic, but apparently without retinal changes (Usher, 1935). In the second pedigree, in which myopia was not present, the heterozygous females had most unusual fundi, exhibiting a tapetal-like retinal reflex which upon ophthalmoscopic examination was shown to be due to the presence in and about the macular area of numerous dust-like, golden glittering bodies (Falls & Cotterman, 1948).

At least seven pedigrees of so-called choroideremia in which there is sex-linked inheritance with changes in the heterozygous females are now known (Smith & Usher, 1916; Zorn, 1920; Schutzbach, 1938; Goedblad, 1942; McCulloch & McCulloch, 1948; Falls, unpublished manuscript). Affected males exhibit a severe type of retinal degeneration with night blindness, progressing in most cases to complete loss of vision, whereas the heterozygous females usually are characterized by a combination of minor pigmentation and depigmentation of the fundus, which may be referred to as atypical retinitis pigmentosa. The most extensive of these pedigrees includes 600 persons (McCulloch & McCulloch, 1948). Here there has been ample opportunity to study women known by the progeny test to be heterozygous. In every case, significant changes are present. Similar changes are seen in certain of the female children who from their position in the family may be assumed to be heterozygous, suggesting that the carriers are recognizable from an early age.

In contrast to the preceding two illustrations, in these sex-linked choroidoretinal degenerations where a carrier state may be recognized, the characteristics of that state must be defined for each individual pedigree, as might be expected from the probable genetic diversity of the included conditions.

Huntington's chorea is a degenerative disease of the central nervous system associated with purposeless involuntary movements and progressive mental deterioration. Onset is usually in the third or fourth decade. Afflicted persons may thus marry and complete their families before the signs and symptoms of the disease make their appearance. The disorder is transmitted as if due to a single dominant factor with a high degree of penetrance (Davenport & Muncey, 1916; Entres, 1921; Meggendorfer, 1923; Hughes, 1925; Geratowitsch, 1927; Vessie, 1932; Bell, 1934; Sjögren, 1935; Minski & Guttman, 1938).

The development of the electroencephalogram has offered a new tool to those interested in the prediction and early diagnosis of mental disease. The occurrence of abnormal encephalograms in the parents and siblings of persons with epilepsy, similar to the tracings in the epileptics themselves, has been recognized for some time (review in Neel, 1947). More recent studies have dealt with the "brain waves" in Huntington's chorea. As might be expected from

the widespread involvement of the brain in this disease, the electroencephalogram of affected persons is markedly abnormal (Gibbs & Gibbs, 1941; Yeager & Baldes, 1937; Foster & Bagchi, unpublished). A recent investigation has been concerned with the electroencephalographic findings in 26 children of patients with Huntington's chorea (Patterson, Bagchi, & Test, 1948). The subjects ranged in age from 6 to 41. Nineteen of these offspring (73.1%) were definitely abnormal. There was no one characteristic finding, but a mixture of findings such as might be associated with a variety of other conditions. It was possible to divide the abnormals into two groups on the basis of a properly weighted treatment of the various types of brain wave aberrations present, one group of twelve subjects in whom the findings were more extreme, and one of seven with lesser findings. The authors felt that these twelve persons were likely to develop Huntington's chorea. The validity of the prediction cannot be fully tested for some 40 years, but if correct its genetic significance is obvious. In this connection it is of interest to point out that in one investigation it was possible to trace some 962 cases of this disease occurring primarily in the eastern costal area of the United States back to some seven persons from four families, including three brothers, who emigrated to American in the seventeenth century and then developed the disorder (Davenport & Muncey, 1916). Even the most hesitant of us to venture into the field of negative eugenics would probably agree upon the desirability of detection and exclusion of such immigrants, on the same grounds that the United States Public Health Service now excludes those infected with certain contagious diseases. From the public health standpoint, one of the most striking differences between disease due to a contagious agent and that due to an hereditary factor is the contrast between a horizontal stratification with familial factors in the background and a vertical stratification with familial factors predominating. Because of the more immediate problems posed by the horizontal distribution, it has been characteristic of medicine to give diseases following this pattern the bulk of the attention.

Time unfortunately does not permit a detailed consideration of any further examples. The four disorders which have been discussed were chosen to illustrate particular points, and especially the manner in which morphological, biochemical, and physiological techniques must be utilized in the definition of carrier states. Other equally pertinent illustrations could have been selected for consideration. However, it must be recognized that by no means all carrier states are as well defined as these four examples. Table 1 lists those conditions in which there is reason to believe that carriers may be detected with varying degrees of accuracy. For some of these examples there is little more to go on than a hint at the present time. In other instances, the possible stigmata of the carrier state become apparent too late in life to be of value in genetic prognosis. From the standpoint of the total medical load, it is obvious that at

the present time the detection of these carriers is certainly not a major adjunct to medical practice. However, in the face of a constantly expanding knowledge

TABLE 1. DISEASES IN WHICH A RECOGNIZABLE CARRIER STATE MAY EXIST

Those diseases in which the carrier state is most clearly differentiated, or in which there is some promise that a clear differentiation may be achieved, are italicized.

A. Metabolic disorders.
   1. *Diabetes mellitus*
   2. *Gout*
   3. *Primary essential xanthomatosis*

B. Diseases of the nervous system.
   4. Amaurotic idiocy
   5. *Epilepsy*
   6. Friedreich's ataxia
   7. *Huntington's chorea*
   8. Phenylpyruvic amentia
   9. Syringomyelia
   10. Pick's disease

C. Diseases of the blood.
   11. Afibrinogenemia
   12. *Congenital hemolytic jaundice*
   13. Congenital hypoprothrombinemia
   14. *Hemophilia*
   15. Ovalocytosis
   16. Pernicious anemia
   17. *Sex-linked hypochromic, microcytic anemia*
   18. *Sickle cell anemia*
   19. *Thalassemia*
   20. Thrombasthenia

D. Diseases of the cardiovascular system.
   21. *Essential hypertension*
   22. Hereditary hemorrhagic telangiectasia

E. Diseases of the skin.
   23. Anhidrotic ectodermal dysplasia
   24. Keratosis follicularis spinulosa
   25. Xeroderma pigmentosum
   26. Ehlers-Danlos syndrome

F. Diseases of the skeleton.
   27. Brachyphalangy
   28. Congenital dislocation of the hip
   29. Morquio's disease

G. Diseases of the eye.
   30. *Choroidoretinal degeneration* (sex-linked)
   31. Color blindness

H. Miscellaneous.
   32. Albinism
   33. Allergy
   34. Laurence-Moon-Biedl syndrome

of the minutiae of man's anatomy, physiology, and biochemistry, it is impossible to hazard a prediction as to the limits of the ability to detect the carriers of genetically determined disease through careful, detailed medical studies.

It is probable that in man the majority of genes will be found to show some effect in the heterozygous state. It may also be taken as a general rule that genes have multiple effects, some more apparent than others. Even so, there will undoubtedly always remain many inherited diseases in which the carriers exhibit absolutely no detectable departure from the norm, or in which the stigmata of the carrier state are so non-specific, as in the case of the abnormal brain waves in the carriers of epilepsy at the present time, that the predictive value is seriously impaired.

III

The possibility of utilizing a genetic linkage between a gene which has slight effects approximating physiological neutrality but whose presence is readily recognized and a gene with more drastic and undesirable effects, which is either recessive or which manifests itself late in life, in order to "tag" the latter gene so that its transmission may be readily followed, has been recognized for many years (Snyder, 1931; Fisher, 1935; Finney, 1940; Muller, Little & Snyder, 1947). Efforts directed at the exploration of this possibility have had to await the development of mathematical techniques appropriate to the study of linkage in man, where one encounters problems which do not arise in the study of linkage in experimental material. Such techniques have now been evolved, largely through the work of the English school of mathematical geneticists (Bernstein, 1931 *et seq.*; Wiener, 1932; Fisher, 1934 *et seq.*; Haldane, 1934 *et seq.*; Hogben, 1934 *et seq.*; Penrose, 1935 *et seq.*; Finney, 1940 *et seq.*). A considerable number of pairs of inherited traits have been tested for the existence of linkage between the genes responsible for them. The tests which have been carried out are of two kinds, those concerned with autosomal linkage, and those concerned with sex-linkage. Table 2 summarizes some of the possible autosomal linkages which have been discovered to date. In the construction of this table, a considerable number of reports have been omitted where the presumed linkage consists of an association, within a single kindred, of two traits, one or both of which may have ill-defined genetic bases. In these cases it is not possible to conclude whether one is dealing with a linkage or the multiple effects of a single gene; there has been considerable confusion on this score. Several of the studies included in the table have utilized characteristics the genetic background of which is still somewhat obscure. Because of the dearth of our knowledge of heredity in man, investigators have not found it feasible to restrict linkage studies to traits with a well defined, unigenic basis. Some of these possible "linkages" are thus on a much more ambiguous footing than the linkages known to Drosophila and maize workers, and in view of our lack of knowledge concerning gene interaction in man, must be accepted with caution. Of the various linkages summarized in the table, that involving the sickle cell trait and the MN blood types is perhaps the best exam-

ple of linkage between a common marker gene and one responsible in some persons for a pathological trait (Snyder, Russel, & Graham, 1947). But since the tendency towards sickling depends on a dominant gene with high penetrance, the carriers may in this instance be determined by simple, direct examination of the blood much more readily than through linkage studies.

The limitations inherent in the "linkage" method of following the genetic carriers of inherited disease, although touched upon by several investigators (Fisher, 1935a; Penrose, 1935), have never been subjected to close scrutiny. Such examination is long overdue. In order for this method to be useful in the

TABLE 2. PROBABLE AND POSSIBLE AUTOSOMAL LINKAGES IN MAN

TRAITS	METHOD USED	P-VALUE	INVESTIGATOR
Red hair—ABO	Sib pairs	0.033	Penrose, 1935
Friedreich's ataxia—ABO	Bernstein's method	?	Hogben & Pollack, 1935; Fisher, 1936; Haldane, 1946.
Congenital tooth deficiency —hair color	Sib pairs	0.025	Burks, 1938
Phenylketonuria—ABO	Sib pairs	0.046	Munro, Penrose, & Taylor, 1939; Penrose, 1946; Haldane, 1948.
Allergy—ABO	Finney's modification of Fisher's *u*-scores	0.045	Zieve, Wiener, & Fries, 1936; Finney, 1940.
Ovalocytosis—ABO	Sib pairs	0.06	Burks & Wyandt, 1941
Palm patterns—handedness	Sib pairs	0.001	Rife, 1941
Ear flare—finger length	Sib pairs	0.008	Kloepfer, 1946
Finger length—eye color	Sib pairs	0.017	Kloepfer, 1946
Ear flare—eye color	Sib pairs	0.001	Kloepfer, 1946
Ear size—PTC	Sib pairs	0.001	Kloepfer, 1946
Cross eyes—hair color	Sib pairs	0.018	Kloepfer, 1946
MN—ear flare	Sib pairs	0.035	Kloepfer, 1946
Eye color—tongue curl	Sib pairs	0.048	Kloepfer, 1946
Sickle cell—MN	Finney's modification of Fisher's *u*-scores	0.02	Snyder, Russel, & Graham, 1947.

prediction of genetically determined departures from normality, a number of rather exacting conditions must be met:

(1) To begin with, there must be available physiologically neutral, or nearly neutral, marker genes for each of the 23 autosomes in man. The markers must be neutral or nearly so, for otherwise they are not markers, but rather deleterious factors whose appearance it becomes desirable to predict. These marker genes must be rather closely linked to the factor whose inheritance is being traced. If, for instance, there is 20 percent recombination between the two factors, genetic prognosis based on linkage relations assumes a high degree of uncertainty. There are at the present time no extensive and really satisfying data on the probable genetic lengths of the autosomes in man, although the best available approximation, based on mean chiasma frequency, would be

an average length of about 100 units (Schultz, unpublished). In the mouse, with 20 pairs of chromosomes, the estimated mean genetic lengths of the autosomes, based on mean chiasma frequency, are 120 units in males and 140 units in females (Crew & Koller, 1932; Huskins & Hearne, 1936). Let us say that something less than 5 per cent of recombination is desirable if a linkage is to be utilized in clinical medicine. Under these circumstances, an autosome 120 crossover units in length needs a minimum of 12 marker genes.

(2) The markers should have a high frequency in the population. Rare markers, with a gene frequency of less than 0.05, are of limited value, since only about 10 percent of the population will possess them. Only nearly neutral genes are apt to have high frequencies.

(3) To be of maximum usefulness, a marker gene should be distinguishable in the homozygous and heterozygous states. In the case of rare markers, one can assume heterozygosity with slight error, so that one avoids this complication. But as pointed out above, the usefulness of the rare markers is limited just by virtue of the fact that they are rare—unless a large number of them are discovered. The occurrence of dominance is a particularly serious drawback when applying the more delicate tests of linkage.

(4) Even if all these conditions are met, only a certain proportion of families, in which there is heterozygosity for the marker, are susceptible to genetic prognosis based on linkage. Thus, given a gene pair where each of the two alleles has a frequency of 0.5, and assuming equilibrium, then 25% of the population would be expected to be homozygous for the one factor, and another 25% homozygous for the other factor, leaving only a half of the population in which the genes will have the desired heterozygosity.

(5) A final complication of linkage studies is the fact that the same phenotype may have several different genetic bases. Under these circumstances it will sometimes be difficult to decide which set of marker genes should be utilized in attempting to follow the transmission of an undesirable gene. Moreover, some of the marker characteristics themselves may have a multigenic basis. This fact is already illustrated in the very tentative maps of the autosomes which have been constructed (Muller, Little, & Snyder, 1946); because of inconsistencies in the data it has been necessary to assign both eye color and ear flare to two different chromosomes, so that each now has two different sets of linkage relations.

In view of the rapid developments in the field of human heredity, and especially in the realm of serology, where special help in the search for marker genes may be forthcoming, it would be very premature to say that the above stated difficulties cannot be overcome. The eventual discovery in man of serological variability such as is now known to exist in cattle (Ferguson, Stormont & Irwin, 1942; Owen, Stormont, & Irwin, 1944) is greatly to be desired. However, it does seem fair to estimate that unless a great many more peo-

ple enter into this type of investigation than are now so engaged, a period of some years must elapse before sufficient marker genes have been accumulated and their positions mapped. But let us assume that the day arrives when we have some 100 marker genes distributed among the 23 pairs of autosomes, or, roughly, an average of five to a chromosome. Let us assume further that the autosomes in man are relatively short, having an average genetic length of 50 units. The actual length may be closer to 100 units (Schultz, personal communication) but we shall use a more conservative estimate, in order to reinforce, for the purposes of this illustration, the usefulnes of the marker genes. What, now, is the potential utility of these five markers in each chromosome? Assume that the markers are equally spaced along the chromosome, with the first 5 units from one end of the chromosome, and assume that each marker has a frequency of 0.5, with the heterozygote readily distinguishable from the homozygote. Only heterozygous individuals are of value to the linkage studies. Under the above outlined very favorable circumstances, there will on the average be heterozygosity for 2.5 markers. With a mean chromosomal genetic length of 50 units, this means an average of 20 percent recombination between the markers and the genes which it is desired to follow. Furthermore, we are faced with great difficulty in two or even three generation pedigrees in determining whether the genes under consideration are in the coupling or repulsion phase. It is one thing to validate a linkage statistically, and another to utilize that linkage in single families. Finally, we face certain losses of information depending on the genetic constitution of the spouse. All of these facts so reduce the usefulness of the method that one is forced to conclude that for some time to come it will only be in the exceptional pedigree, where three of more generations can be studied and there is known close linkage, that the fact of linkage will be of value to the prediction of which individuals in a population may be expected to develop disease due to an autosomal gene.

The situation in regard to sex-linkage is somewhat different. There have now been described some thirty definitely sex-linked traits, and an additional eight showing incomplete sex-linkage (Gates, 1946; Muller, Little, & Snyder, 1947). The fact that all these factors are situated on the sex chromosome results automatically in their genetic linkage, although if the observation of two sex-linked genes with 50 percent recombination is verified (White, 1940), this linkage need not be close. But the known genes are so rare that up to the present time little progress has been made in mapping the sex chromosome, since the presence of any two of these genes in the same pedigree, a situation prerequisite to mapping the position of the completely sex-linked genes, is unusual. Two of the most common, clearly defined, sex-linked genes are those responsible for hemophilia, which trait has a frequency of approximately 0.013 percent in European males and is probably unknown in females

(Andreasson, 1943), and for color blindness, which trait, including all types, occurs in 7.95 percent of European males and 0.3 percent of European females (von Planta, 1938). The frequency of color blindness is of course well below the optimum for a marker gene. The literature contains some seventeen pedigrees in which both these traits were segregating in the same pedigree (Madlener, 1928; Davenport, 1930; Bell & Haldane, 1937; von Rath, 1938; Riddell, 1938, 1946; Hoogvliet, 1942). The maximum likelihood estimate of the frequency of recombination between the two genes is 9.8 percent, and the probability is 0.9 that the true recombination value lies between 5 and 20 percent (Haldane & Smith, 1947). A single pedigree is on record in which a woman heterozygous for hemophilia and color blindness, with the two factors in all probability located on the same chromosome, married a color blind man. Her children consisted of five daughters, one color blind and four with normal vision. It has been stated that the color blind woman has a probability of 0.9 of carrying the hemophilia gene; if she does carry the gene, half of her male children will of course be expected to have hemophilia. But for the sisters with normal vision the probability is only 0.1 that they receive the gene for hemophilia (Hoogvliet, 1942; Haldane & Smith, 1947). This statement does not take into account the fact that the gene for color blindness produces phenotypic effects in a small proportion of heterozygous females (Bell, 1926). To date this is the best illustration of prediction by linkage methods. Inasmuch as some 95 percent of women who have hemophilic sons themselves appear to show a significant prolongation of coagulation time (Schloessmann, 1924; Günder, 1938; Andreassen, 1943), it appears that in the case of hemophilia the detection of carriers will, for some time to come, be best accomplished by clinical means.

IV

The implications of more efficient methods of detecting genetic carriers, whether by linkage or clinical studies, are manifold. As the ability to diagnose carriers improves, there will inevitably result an extension of our knowledge of specific genes, whose frequencies may be accurately surveyed. The physical anthropologist, who more and more is interested in defining the subdivisions of man in terms of genetic constitution, will thus find himself provided with numerous new tools. The diligent application of these cannot fail to shed light on the interrelationships of the various groups of which man is composed, and this a good deal more successfully than could be expected through further refinements of measurements of physical differences (*cf.* Boyd, 1947). But perhaps of equal significance to the light thrown on developments of the past will be the demonstration of the extent of man's present genetic disequilibrium, with its connotations for the future. Parenthetically, it might be pointed out that the distinction between the anthropologist who appreciates the significance of recent genetic developments and is applying them, and the

geneticist interested in gene frequencies and their phenotypic counterpart in human populations, is one which is increasingly difficult to maintain.

Students of physiological genetics have never been overly impressed by the opportunities which man offers for their researches. To a large extent this attitude can only be attributed to a lack of familiarity with the vast store of information available concerning the biochemistry and physiology, as well as the anatomy, of man. It is true that pure strains of various inherited disorders do not exist. It is also true that embryological series are difficult to assemble. But any large medical center has on file a considerable number of people with all manner of defects except the very rare. Such persons are usually cooperative. The precision with which their metabolic processes may be defined, in comparison with flies, mice, or even Neurospora, is probably not fully appreciated by many geneticists. The clinical recognition of early carrier states provides a wealth of material for the investigation of genetically controlled transition stages between the normal and the grossly abnormal.

The sociological implications of the possibility that we may some day be in a position to detect a high proportion of the genetic carriers of many inherited diseases bear a searching examination. For with this detection there arise new lines of approach in the field of preventive medicine, and the sociological consequences may be far reaching. This general topic is one which should be treated adequately if at all; in view of our time limitations today, it seems best not to embark on any such discussion.

V

The foregoing consideration has been directed towards an evaluation of the present state of our knowledge in one of the major areas of interest to the human geneticist at the present time. It would have been equally appropriate at a meeting of this nature to attempt to evaluate and sharpen our perspective on any one of a number of other major problems facing human geneticists and those with cognate interests. For instance, we might have discussed the problem of mutation, or the problem of defining the groups of man in terms of gene frequencies, or the question of the types of selection operating in present day society, or the relation between gene and phenotype, and the possible modifications of this relation. In any such discussion we would have found, just as in the present instance, that we immediately impinged on the interests of many different disciplines. The study of heredity in man ramifies through all of human biology. No matter what his starting point, an individual interested in a problem in human heredity is apt to find that he has been led through an intricate nexus into an area where his competence is dangerously low. This is particularly true in the field of medicine. Human geneticists, except perhaps those interested exclusively in the mathematical, formal genetics of man, will therefore more and more function as members of a team in-

vestigating a complex problem. Their role on these teams consists of much more than analyzing data which others have collected. It will be necessary to take a very active hand in directing the accumulation of these data in order that they conform with genetic standards. As has been frequently pointed out, too many of the pedigrees in the literature are deficient on critical points. This brings us to a note on which I would like to conclude. There is a tendency in some quarters to regard the accumulation of pedigrees on all sorts of inherited conditions, the descriptive genetics of man, as "old fashioned". But the spectacular contributions of Drosophila studies to the science of genetics depended primarily on the fact that it was possible in a short period of time to accumulate and accurately describe a large number of inherited traits, which then served as the tools for further investigations. There will be few to dispute the assertion that the greatest overall need in the field of human genetics at the present time is the more accurate definition of what is and what is not inherited, through the accumulation of reliable descriptive material. The solution of many problems, or at least a step in that direction, will then follow automatically.

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Hereditary Nerve Deafness[1]

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INTRODUCTION

THE present study was undertaken by a geneticist and an otolaryngologist when hereditary nerve deafness, occurring in later life, was discovered in a large Utah kindred. Little work had been done previously on the inheritance of this type of deafness. Detailed family records for 319 members of the kindred were secured and charted for analysis. Whenever possible these records were supplemented by examinations, including audiograms. Where it was necessary to depend upon members of the family for data, the reliability of the information was carefully checked by additional inquiries.

The type of deafness as well as possible contributing factors have been investigated. The nature of its inheritance has been determined, and a record of other hereditary traits such as blood groups and taste deficiency has been made. It is planned to consider their possible linkage relationships in a later report. The families were very much interested in the study and gave excellent cooperation.

Historical Background

There are four types of deafness in which genetic factors may be operative: (1) congenital deafness resulting in deaf mutism; (2) otosclerosis; (3) familial deafness caused by otitis media; and (4) a hereditary form of nerve deafness appearing in later life.

Most attention has been focused heretofore on the first three types. The study of congenital deaf mutism received a tremendous impetus when Helen Keller showed that children with this handicap could be taught to speak. As a result, many schools for the deaf were established where studies have been made on deaf mutism. These suggest that the inheritance is recessive and is due to one, or possibly to either one of two recessive factors (Lindenov, 1945; Hopkins, 1946; Macklin, 1946).

Much interest was centered on otosclerosis when Lempert (1938) revived the fenestration operation and was able to restore hearing in a number of cases. Otosclerosis is not actually a disease of the ear. It is a disease of the temporal bone in which a bony proliferation may either obstruct the action of the ossicles, usually at the oval window, or compress the nerve in the cochlea. The disease also may occur in silent areas of the temporal bone and then there is no auditory involvement recognizable by clinical procedures. Consequently, until serial sections of the temporal bones of all members of families having otosclerosis are examined at autopsy, it will be very difficult to establish the exact hereditary pattern of such a kindred. In genetic studies, otosclerosis has been reported as being due both to

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dominant inheritance and to the combination of an autosomal dominant and a sex-linked dominant (Davenport *et al.*, 1933; Amidon, 1948).

Otitis media probably accounts for the greatest percentage of deafness. While most otologists consider that otitis media occurs in certain families, they do not agree that this is entirely due to hereditary factors. It is possible that the tendency of lymphoid tissue to hypertrophy in the vicinity of the Eustachian tubes may be inherited or that a greater susceptibility to infection of the mucous membranes of the middle ear may have a similar basis. However, these are, at most, only two of the contributing factors.

The fourth type of hereditary deafness, the nerve impairment of later life, has not been thoroughly investigated previously. Ten family pedigrees reviewed by Albrecht (1922) ranged from a family with three members affected in two generations to a family with nine members affected in five generations. Of the latter family the first three generations were not available for testing. In the absence of complete information, Albrecht assumed the pattern to be that of a dominant. It is not quite clear from his article at what age the deafness commenced. Other short studies based on a few cases have been reported from time to time (Shambaugh & Shambaugh, 1933; Dean & Bunch, 1923; Eagleton, 1946; Popov, 1935). An opportunity to supplement this knowledge was provided by the willingness of a large family suffering from the ailment to present itself for study.

DECRIPTION OF KINDRED STUDIED

Figure 1 gives the pedigree of a large Utah kindred showing nerve deafness in six generations.

The first member known to show the trait was *I-1*. He was born in England in 1788 and died in Utah in 1877. Three of his seven children are reported to have been deaf. The condition of the other four is unknown. Of the 319 descendants of *I-1* about whom information was obtained, 72 are known by history or examination to have been deaf. Of these, 62 were thought to have hereditary nerve deafness and ten to have other forms of deafness. In addition to this group, 19 individuals show high tone deficiency in varying degrees, but are not deaf within the normal range of the spoken voice.

No information is available regarding the parents of the original progenitor, *I-1*, nor of members of his family who remained in England. His descendants have become scattered throughout the United States. The large majority, however, reside in Utah and were available for study.

On the chart, individuals who died in infancy or childhood and those who are twenty-five years of age or under are indicated by smaller circles or squares. These individuals could not be safely classified because the trait seems to emerge at approximately the mid twenties. Those showing types of deafness other than the hereditary nerve deafness are distinguished by circles and squares which are only partially filled. A small cross (x) below the circle or square indicates that the individual underwent examination and that audiometric readings were taken. Those showing high tone deficiency are represented by circles and squares which are lined. Examples of the audiometric readings for the different groups are shown in figure 2.

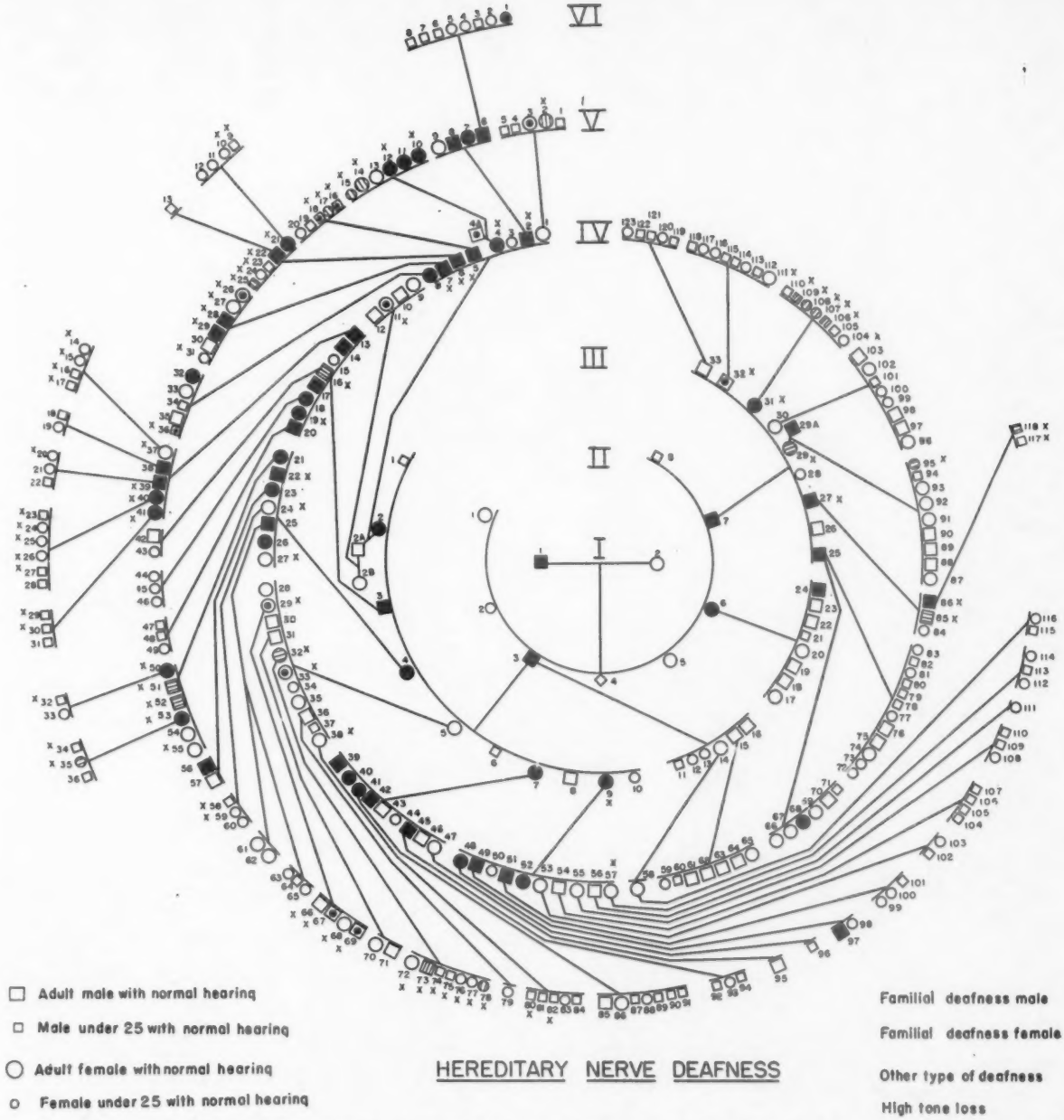

FIG. 1. Pedigree of Utah kindred showing hereditary nerve deafness. (Stephens, F. E., & Dolowitz, D. A. 1949. *Am. J. Human Genet.* 1(1): 37–51.

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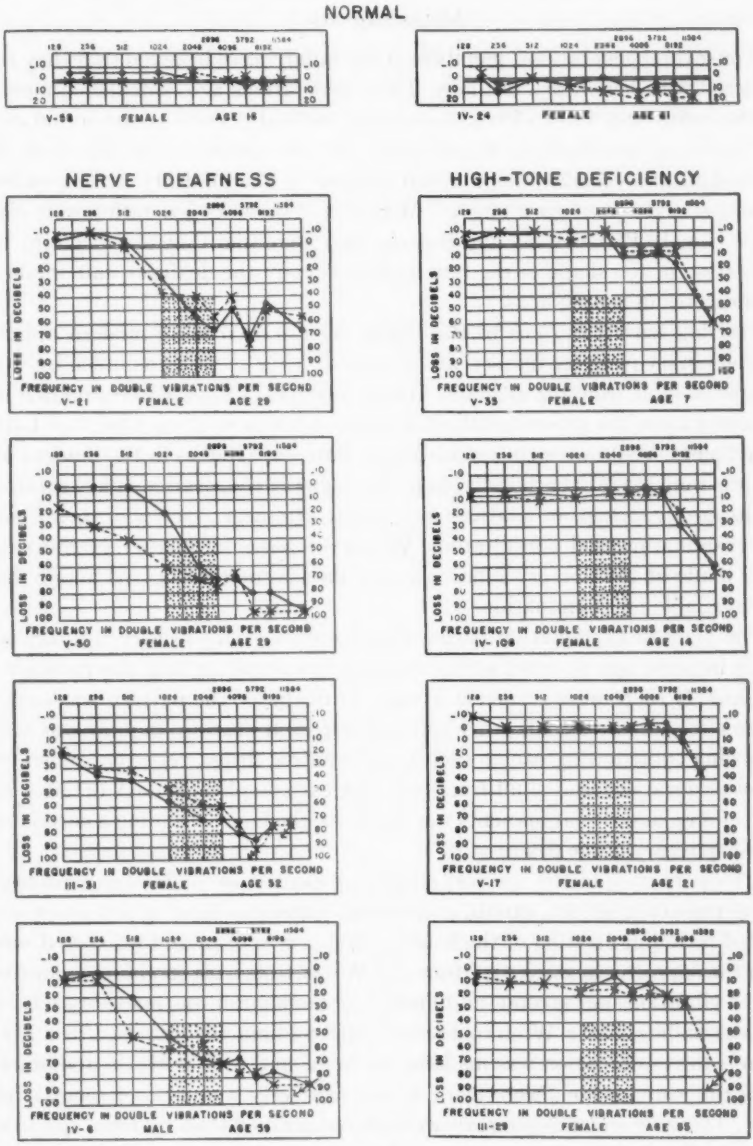

FIG. 2. Representative audiograms for cases of hereditary nerve deafness and high-tone deficiency.

Methods of Study

For several generations, members of the family have believed that they were afflicted with hereditary deafness. Three generations ago, a deafened member of the family was sent to Paris to see if the medical sciences of the period could aid either in treatment or in prevention of this condition. He was told that "his skull had certain bumps which pressed on the auditory nerves, causing deafness as the head grew larger". Members of the next generation were given more hope in Philadelphia and Boston; they were told that tonsillectomy and alteration of the shape of the bite would alleviate the deafness, but would be of most use in prophylaxis.

Starting with a nucleus of the family who desired more modern opinion, a preliminary pedigree history was obtained. After securing as much information as possible from the available known relatives, additional information was obtained from the genealogical office of the Church of Jesus Christ of Latter Day Saints. Visits were then made to the different families in the kindred and records were made of each individual. Through the cooperation of key members of the family, groups of relatives were invited to meet in a few of their homes for examination and consultation. Whenever possible, further examinations were made at the doctor's office. Genetic data were also secured about those not available for examination.

The medical examination began with the taking of a history. Inquiry was made into the age of onset of the deafness, its duration, and the presence of tinnitus. If there were recurrent attacks of deafness, the pattern was sought. In an effort to sift out all other types of impaired hearing, inquiry was made regarding contributing causes such as detonation, drugs, recurrent infections, drum perforations and skull fractures with ear complications. A detailed history of nose and throat ailments was taken, in the hope of finding a correlation with hereditary nerve deafness.

After palpation of the cervical glands, an electric otoscope was used to examine the external ears, canals, and drums. Extensive hearing tests were conducted including: testing of the hearing ability of spoken and whispered voice with the opposite ear masked; Rinne and Weber tests with steel forks vibrating at 512 vibrations per second; and finally, an audiogram was made of each ear. For the audiograms a Western Electric 6BP audiometer was used in a quiet room if the examination was made in the home and with a Macio audiometer when the examinations were made in the relatively sound-proof room at the office. The nose and nasopharynx were then examined both by nasal speculum and an electric nasopharyngoscope. Vestibular examinations were not performed as it was thought that the small amount of information elicited would not be worth the discomfort and possible resulting antagonism that the induced vertigo would produce. The mouth, teeth, tongue, tonsils, pharynx, and larynx were examined with the help of tongue blade and laryngeal mirror.

To establish the accuracy of the hearing tests, five members of the family were rechecked about three months after the first examinations, without reference to the original data. In all cases the two reports were well within the limits of error, i.e., about five decibels for any tone in the audiogram.

Including these five repeat tests, 103 examinations were made. The 98 tested subjects included 93 descendents of *I-1* and five of their spouses. Table 4 gives a detailed summary of the results of the examinations.

Decription of the Trait

Studies of this family show the trait to be a form of nerve deafness with a noticeable onset in the early twenties. It may begin in one or both ears, but usually progresses to become bilateral. The severity of the affliction seems to increase with age until many subjects require a hearing aid in later life, although

TABLE 1.

AGE GROUP	NORMAL	HIGH TONE LOSS	HEREDITARY NERVE DEAFNESS			
			Mild	Moderate	Moderately Severe	Severe
1–9	6	2	0	0	0	0
10–19	18	7	0	0	0	0
20–29	10	3	1	2	1	0
30–39	4	2	2	2	1	0
40–49	2	2	1	0	0	2
50–59	1	2	0	1	2	2
60–69	1	1	0	0	0	3
70–79	0	0	0	1	0	1
Total.....	42	19	4	6	4	8

subtotal deafness does not occur. About a third of the deafened have an accompanying transient tinnitus.

A group of individuals was found ranging between the deaf and the normal, who showed high tone loss while hearing for spoken voice was normal. Several of these volunteered the information that, over a period of years, when listening to orchestras, they were progressively losing portions of the violin music.

Of the 93 tested, 19 showed a high tone loss, 22 showed nerve deafness, 10 were deaf from other determinable causes, and 42 had normal hearing. Although high tone loss is known to have many causes, there is evidence from this study, as will be pointed out later, that it is also a precursor of hereditary nerve deafness. Since single examinations are not sufficient to substantiate the exact cause of the high tone loss, it is being considered in a separate category. If we accept this hypothesis, it is interesting to note that the severity of the trait increases with age, as is shown in table 1.

While high tone loss was present at all ages, it occurred most frequently in

the second decade. Of the seven individuals showing high tone loss later than later than thirty years of age, in only one was the audiogram such that it might be interpreted as being an early indication of the family trait. In the remaining individuals causes other than heredity could be assigned on the basis of history and examination. As the precursor diminishes, the mild hearing loss is seen to begin in the third decade and to last to the fifth; moderate loss of hearing is experienced from the third to sixth decades; moderately severe loss extends from the third to sixth decades, with increases in the later decades; severe deafness appears in the fifth decade, but increases to the seventh, with only one case in the eighth decade. The decrease in the eighth decade is probably due to the natural limitation of the members of this age group. These data will imply that the earliest deafness appears as a high tone loss.

It is interesting to speculate whether the trait represents a premature speeding-up of the aging process of the auditory mechanisms as compared with that of the organism as a whole. This hypothesis is strengthened by the appearance of the audiograms.

As an interesting side-light, an analysis of the ten cases of other types of deafness is offered. Five (*IV-29*, *IV-33*, *V-26*, *V-36*, *V-69*) were conductive hearing impairments. Three of them (*IV-29*, *IV-33*, *V-36*) resulted from repeated otitis media, one of which (*IV-29*) had been treated with quinine. The fourth (*V-26*) was due to otitis media plus malocclusion. The last (*V-69*) is an adenoid deafness in an adult with a deviated septum. Of the remaining five cases, three (*III-32*, *V-16*, *V-18*) showed acoustic trauma, one in a miner (*III-32*) who detonated charges and the other two (*V-16*, *V-18*) as the result of gun fire in military service. Audiograms of these three were characterized by a V-shaped dip centering at about 4096 double vibrations. The last two cases (*V-3*, *V-67*) showed mixed deafness as a result of fractured skulls with torn drums that bled for some days after the injury.

Possible Role of Other Factors

An attempt was made to see if the occurrence of the deafness could be correlated with the presence of infected tonsils, adenoids, allergy, malocclusions, septal deflections, sinusitis, or the lack of teeth, even where partially compensated by plates. An analysis of these studies follows:

Tonsils. Of the 93 cases studied, 14 had normal tonsils. Approximately fifty per cent of these had normal hearing and twenty per cent had family deafness. Of the 59 in whom tonsillectomy had been done without regrowth or infection, forty-six per cent had normal hearing and twenty-seven per cent were deaf. Those with infected tonsils could be grouped similarly in these categories and show approximately the same figures, the differences being non-significant. The relevance of the data is weakened because the family had been told that the presence of tonsils contributed to or caused the deafness; therefore many submitted to tonsillectomy as soon as they realized they were becoming deaf. In view of the figures obtained, and the artificial increase in the number of tonsillectomies in the deafened, it is thought that the presence or absence of tonsils is not relevant to the family deafness.

Adenoids. In a study of the nasopharynx, 31 of the 93 persons examined were found to have hypertrophied adenoid tissue. Only two of these showed the family deafness, and seven a high tone loss. It is interesting that in the five cases of high tone loss which we selected as showing the familial trait, all had small adenoids not obstructing the Eustachian tubes. It would thus appear that adenoids have no effect on this type of hereditary nerve deafness.

Allergy. Twenty-seven of the 93 individuals studied gave a history of allergy, especially hay-fever (29%). Of the 22 deaf individuals, seven (32%) gave an allergic history. This suggests that allergy has no effect on the expression of this trait.

Malocclusion. Ten cases of malocclusion were found. Five of the subjects had high tone or other types of deafness; none had the family deafness.

Deviated Septum. Of the 93 individuals examined, 32 (34.4%) had deviated septums. This seems a high proportion. Of these 32 individuals, ten (31.25%) had hereditary nerve deafness, compared with (23.6%) in the total group. This higher percentage of deafness in those with septal deflection could be explained if the irregular septums were hereditary, although not necessarily related to the deafness. There is evidence that the septal deviation is inherited since, in some cases, it could be followed through three generations. However, before definite conclusions regarding its hereditary nature can be drawn, further examinations of both parents and children would have to be made. It is difficult to believe that septal deflection could play a significant role as the cause of hereditary nerve deafness.

Sinusitis. Of the 93 individuals examined, 17 were found to have sinusitis. Of these 17 individuals, only one showed family nerve deafness. This would suggest that sinusitis played no part as a cause of this type of deafness.

Loss of Teeth. While 19 of the 93 studied cases are edentulous, only one of the group retains normal hearing. At first glance, this would imply that loss of teeth, altering the bite, even if plates are used, is a marked factor in causing the deafness. Further examination, however, shows that the edentulous group is composed of older individuals in whom severe deafness predominates. Furthermore, in this age of indiscriminate extractions, some had teeth removed in an attempt to prevent progressive deafness. Despite all these factors, it is hard to explain why only one of the 19 edentulous persons had normal hearing. The need for further study is indicated.

Inheritance of the Trait

The consealment of the hearing mechanism within the bony skull structure affords protection against injury, but also makes it difficult to detect the locality of any defect. In general, disease, environmental injury, or the action of a defective gene may produce deafness. In the case of a hereditary hearing impairment, it is possible that any one of a number of genes, or a combination of several, may affect the ear.

Hereditary deafness, as shown, need not appear at birth. It is possible that the determining factor may be an inherited tendency to the premature aging of a specialized structure. This view was strengthened by study of the audiograms.

The characteristics of the form of hereditary deafness found in this kindred present some problems in determining its inheritance. Since the age of onset was usually between twenty and thirty years and varied considerably, the younger members of the families, as noted above, cannot be classified accurately Where it was impractical to examine all members of a family and infor-

mation had to be secured from a few members, the less severe cases of deafness may have been missed. Those showing high tone deficiency would have been entirely overlooked, and only the more severe remembered. In a few individuals other types of deafness occurred, and in certain instances individuals marrying into the family may have brought in factors influencing hereditary deafness. Thus the husbands of *III-29* (*III-29A*) and *IV-4* (*IV-4A*) are both deaf. *III-29A* could not be examined; *IV-4A* at examination was found to have nerve deafness, but the age of onset was much later in life than in those with

TABLE 2. CLASSIFICATION OF OFFSPRING IN TWENTY-TWO SELECTED FAMILIES

PARENT	CHILDREN									
	Hereditary Deafness		Conductive or Other Deafness		High Tone Deficiency		Normal		Condition Unknown	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
II-3	1	4	—	—	—	—	1	1	2	1
II-3	—	—	—	—	—	—	2	1	1	2
II-7	2	1	1	—	—	1	2	1	—	1
III-2	4	2	—	—	—	—	—	—	—	2
III-4	2	3	—	—	—	—	—	2	—	—
III-7	3	2	—	—	—	—	2	1	—	1
III-8	4	2	1	—	—	—	—	—	—	1
III-9	2	2	—	—	—	—	2	3	—	1
III-27	1	—	—	—	1	—	—	—	—	—
IV-2	2	1	—	—	—	—	—	1	—	—
IV-4	—	3	—	—	—	2	—	1	—	—
IV-5	—	—	1	—	1	1	—	—	1	1
IV-6	1	1	—	—	1	—	1	1	—	—
IV-7	2	—	—	1	—	—	—	1	1	1
IV-8	—	1	1	—	—	—	1	1	1	—
IV-13	2	2	—	—	—	—	—	1	—	—
IV-18	—	—	—	—	—	—	—	3	—	—
IV-20	—	—	—	—	—	—	2	1	—	—
IV-21	1	2	—	—	1	—	—	2	—	—
IV-23	1	—	—	—	—	—	1	—	—	—
IV-25	—	—	—	—	—	—	1	4	—	—
IV-49	1	—	—	—	—	—	—	1	—	—
Total.....	29	26	4	1	4	4	15	26	6	11

the typical family deafness. Many accidental factors may introduce non-hereditary types of hearing impairments in individual cases.

In an attempt to eliminate as many conflicting situations as possible, 22 families in the kindred were selected about whom our information seemed complete and accurate enough to permit reliable conclusions. The members of these families are classified in table 2.

It will be seen that of the 126 offspring in this group, 55 are classified under hereditary deafness, five under conductive and other types of deafness, eight

under high tone deficiency, 41 under normal hearing, and 17 under "condition unknown". The question arises whether the 13 individuals listed under other types of deafness or under high tone deficiency should be classed with those having normal hearing, or whether they belong instead with the hereditarily deaf.

The five classified under other types of deafness (*III-32*, *V-16*, *V-18*, *V-26*, *V-36*) and three of those classified under high tone deficiency (*III-27*, *III-29*, *IV-16*) were included with the normal, as it was thought they did not show the family trait. The other five (*V-14*, *V-15*, *V-19*, *V-25*, *V-52*) were included with the hereditarily deaf. The three showing high tone deficiency who were classified with the normals were considerably past the age where deafness generally occurred in the family. The other five who were classified with the deaf were young and it was thought that they would probably become deaf a little later in life. However, this was a somewhat arbitrary decision, the correctness of which can be determined only by future examinations. At all events, these numbers are insufficient to make any significant difference in the calculations. This high tone deficiency not only was found in families where deafness

TABLE 3

	OBSERVED		TOTAL OBSERVED	CALCULATED	DEVIATIONS	S. E.	DEV./S. E.
	Males	Females					
Deaf	31	29	60	54.5	5.5	5.22	1.05
Normal hearing	21	28	49	54.5	5.5		

occurred, but in some instances where the regular family hereditary type was not present. It may be caused by factors other than the defective gene. It is hoped that after a few years have elapsed these questionable cases can be reexamined.

The general picture as indicated in the pedigree chart is one of dominant inheritance for the trait. Since the matings are with very few possible exceptions between a deaf and normal parent, a 1:1 ratio would be expected. Table 3 shows the data classified on this basis:

The deviations are not significant; the results indicate simple dominant inheritance. Since in no case does a child show the trait unless one of his parents also shows it, the penetrance is complete. A person showing the trait will transmit it, on the average, to one-half of his children. Individuals not showing the trait will not transmit it. What at first appeared to be an exception to this was the case of *III-2A*. By his first wife who was a member of the kindred he had several deaf children. By his second wife *III-2B*, who was not a member of the kindred, he had another deaf daughter, *IV-2*. Examination, however, showed her to have conductive deafness and not the family hereditary type.

TABLE 4. SUMMARY OF RESULTS OF EXAMINATIONS FOR HEREDITARY NERVE DEAFNESS

NUMBER	AGE	AGE OF ONSET	SEVERITY	OTHER TYPES OF DEAFNESS	TONSILS	ADENOIDS	ALLERGY	MALOCCLUSION	DEVIATED SEPTUM	SINUSITIS	EDENTULOUS	TINNITUS	NOTES
III-9	77	25	Severe	—	—	—	—	—	—	—	+	+	Incised, scarred drum
III-27	59	35	Mod.	—	+	—	—	—	+	—	+	—	
III-29	55		—	Mild High-tone	+I	—	+	—	+	+	+	—	
III-31	52	40-50	Severe	—	+	—	+	—	—	—	+	—	
III-32	47		Other Type	Mild Acoustic Trauma	+	—	—	—	+	—	+	—	
IV-2	71	30	Mod.	—	—	—	—	—	+	—	+	+	
IV-4	63	30	Severe	—	+	—	—	—	+	—	+	+	
IV-5	61	20	Severe	—	+I	—	+	—	+ (SMR)	—	—	—	
IV-6	59	32	Mod. Severe	—	—	—	+	—	+ (SMR)	—	—	—	
IV-7	56	16	Severe	—	—	—	—	—	—	—	+	—	
IV-16	60		—	Moderate High-tone	+	—	—	—	+	—	+	—	
IV-19	53	20–30	Mod. Severe	—	—	—	—	—	+ (SMR)	—	+	+	Drums scarred and thickened
IV-22	65	25	Severe	—	—	—	—	—	+ (SMR)	—	+	—	
IV-24	61		Normal	—	—	—	—	—	—	—	+	—	
IV-27	55		Normal	—	—	—	—	—	—	—	—	—	
IV-29	61	15	Other Type	Marked conductive rt; mild lf.	+I	+	—	—	—	—	+	+	Eustachean salpingitis
IV-32	56		—	Mild High-tone	—	+	—	—	+	—	+	—	
IV-33	53	16	Other Type	Mild conductive right	RI	+	+	—	—	+	—	+	Rt. ear drained as child
IV-38	44		Normal	—	+	+	+	—	—	—	—	—	
IV-57	31		Normal	—	+I	+	—	—	—	—	—	—	
IV-85	32	Unknown	—	Very mild High-tone	—	—	—	—	+	—	+	—	
IV-86	30	20	Mild	—	+I	—	—	—	—	—	+	+	Scarred right drum
IV-95	15	10	—	Moderate High-tone rt.	—	+	+	—	—	—	—	—	—
IV-104	22		Normal	—	—	—	—	+	—	—	—	—	

IV-104	22		Normal	—	—	—	—	+	—	—	—	—	
IV-106	17	Unknown	—	Very mild High-tone	—	+	—	—	—	—	—	—	
IV-107	15	Unknown	—	Very mild High-tone	+	—	—	+	+	—	—	+	
IV-108	14	12	—	High-tone Cond. with colds	+I	+	—	—	—	—	—	—	
IV-109	10		—	High-tone	+I	+	—	—	+	+	—	—	
IV-110	7		Normal	—	+I	+	—	—	—	—	—	—	
IV-111	26		Normal	—	+I	—	—	—	—	—	—	—	
V-2	43	Unknown	—	Mild High-tone	—	—	—	+	—	—	—	—	
V-3	42	12	Other Type	Mixed right High-tone left	+	—	—	—	—	—	+	—	Skull fracture with torn drum
V-10	40	30	Mild	—	—	—	+	—	—	+	—	—	Drums show calcified scars
V-12	32	25	Mod.	—	—	—	—	—	—	—	—	—	Drums show calcified scars
V-14	27	Unknown	—	Mild Inf. High-tone	—	—	—	—	—	+	—	—	Myringotomy, healed
V-15	20	Unknown	—	Mild High-tone	—	—	—	—	—	—	—	—	Myringotomy
V-16	22	Unknown	Other Type	One ear Mild Noise Deafness	—	—	+	+	—	—	—	—	
V-17	21	Unknown	—	Very mild High-tone	—	—	+	—	—	—	—	—	
V-18	17	15	Other Type	Mild Noise Deafness	—	+	—	—	—	+	—	+	
V-21	29	20	Mod. Severe	—	—	—	+	—	—	—	+	+	
V-22	25	Unknown	Mod.	—	—	—	+	—	+	—	—	—	

+ indicates presence of abnormality; I indicates tonsillar infection; R = Recurrent; SMR = Sub-mucous resection:

TABLE 4. *Continued*

NUMBER	AGE	AGE OF ONSET	SEVERITY	OTHER TYPES OF DEAFNESS	TONSILS	ADENOIDS	ALLERGY	MALOCCLUSION	DEVIATED SEPTUM	SINUSITIS	EDENTULOUS	TINNITUS	NOTES
V-23	23		Normal	—	—	+	+	—	—	—	—	—	
V-24	20		Normal	—	—	—	+	+	—	—	—	—	Prognathous jaw
V-25	18	Unknown	—	Mild High-tone	—	+	+	—	—	—	—	—	
V-26	30	18	Other Type	Mod. Conductive Infection	—	—	—	+	+	—	—	—	
V-27	31		Normal	—	—	—	—	—	—	—	—	—	
V-28	30	Unknown	Mod.	—	—	—	—	—	—	—	—	—	
V-29	28	18	Mild	—	—	—	—	—	—	—	—	—	
V-31	15		Normal	—	—	—	—	+	—	—	—	—	
V-36	23	7	Other Type	Mod. Mixed right Mod. Nerve left	—	+	—	—	—	—	—	—	Scarlet Fever Cond. Noise D.
V-37	44		Normal	—	—	—	—	—	—	—	—	—	Multiple Telangiectasis
V-39	39	Unknown	Mod.	—	—	—	—	—	+	—	—	—	
V-40	33	30	Mild	—	—	+	—	—	—	—	+	—	Appeared with fourth pregnancy
V-41	29	15	Mod.	Infection left acoustic Trauma	—	+	—	—	—	—	—	—	
V-50	42	20	Severe	—	—	—	+	—	—	—	—	+	
V-51	40	Unknown	—	Moderate High-tone	RI	—	—	—	+	—	—	—	
V-52	38	Unknown	—	Mild High-tone	—	—	—	—	+	+	—	—	Broken nose; Calcified scar
V-53	34	20	Mod. Severe	—	RI	—	—	—	+	—	—	+	
V-55	24		Normal	—	—	—	+	—	—	+	—	+	

V-58	16		Normal	—	—	+	+	—	—	—	—	—	
V-59	24		Normal	—	—	—	—	+	+	—	—	—	Moderate overbite
V-66	30	18	Other Type	One ear Cond. Mod. Severe	—	—	+	—	+	+	—	+	
V-67	31		Normal	—	—	—	+	—	—	—	—	—	Draining ears intermittently
V-68	27	Unknown	Other Type	One ear Cond. Mod. Severe	+I	+	—	—	+	—	—	—	
V-71	31		Normal	—	+	—	+	—	—	—	—	—	
V-72	28		Normal	—	—	—	—	—	+	+	—	—	
V-73	24		Normal	—	—	—	—	—	+	+	—	—	
V-74	22		Normal	—	—	—	+	—	+	+	—	—	
V-75	21		Normal	—	—	—	—	—	—	—	—	—	
V-76	17		—	Mild High-tone	+I	—	+	+	—	—	—	—	Had flu at exam Rt. drum dull
V-77	15		Normal	—	—	—	—	—	—	—	—	—	
V-79	18		Normal	—	+	—	—	—	+	+	—	—	
V-81	14		Normal	—	+	—	+	—	—	—	—	—	
V-116	10		Normal	—	RI	+	—	—	+	—	—	—	
V-117	6	Unknown	—	Mild High-tone	—	+	—	—	+	—	—	—	
VI-5	10		Normal	—	+I	+	—	—	—	—	—	—	Poor oral hygiene
VI-9	9		Normal	—	—	+	—	—	+	+	—	—	Hearing cleared with radium
VI-10	7		Normal	—	+	+	—	—	—	—	—	—	
VI-14	18		Normal	—	—	—	—	+	—	+	—	—	
VI-15	17		Normal	—	—	—	+	—	—	—	—	—	
VI-16	11		Normal	—	—	+	+	—	—	—	—	—	Deaf; hearing restored with radium
VI-17	8		Normal	—	—	+	—	—	—	—	—	—	
VI-20	15		Normal	—	—	—	—	—	—	—	—	—	Carious tooth
VI-23	13		Normal	—	+	+	—	—	—	—	—	—	
VI-24	11		Normal	—	+I	+	—	—	+	—	—	—	Carious teeth

TABLE 4.—*Concluded*

NUMBER	AGE	AGE OF ONSET	SEVERITY	OTHER TYPES OF DEAFNESS	TONSILS	ADENOIDS	ALLERGY	MALOCCLUSION	DEVIATED SEPTUM	SINUSITIS	EDENTULOUS	TINNITUS	NOTES
VI-25	9		Normal	—	+	+	—	—	—	—	—	—	
VI-26	7		Normal	—	+I	+	—	—	—	—	—	—	
VI-27	5		Normal	—	+I	+	—	—	—	—	—	—	
VI-29	10		Normal	—	—	—	—	—	—	+	—	—	
VI-30	8		Normal	—	—	—	—	—	—	+	—	—	
VI-32	11		Normal	—	—	+	+	—	+	—	—	—	Myringotomy & repeated otitis
VI-34	11		Normal	—	—	—	—	—	—	—	—	—	
VI-35	7		—	Mild to Mod. High-tone	R	—	—	—	—	—	—	—	
Husband *IV-4*	67	60–70	Mod.	—	+I	—	—	—	—	+	+	—	
Wife *IV-2*	68	Unknown	Mild	—	—	—	—	—	—	+	—	—	
Wife *IV-5*	51		Normal	—	+	—	+	—	+	+	—	—	
Husband *IV-29*	62	Unknown	Mod.	Blasting	+I	—	—	—	—	—	+	—	
IV-11	55	20	Mod.	Otosclerosis	—	—	—	—	—	—	—	+	

SUMMARY AND CONCLUSIONS

1. A study has been made of a large Utah kindred showing hereditary nerve deafness beginning in later life. This disorder heretofore has received little attention.

2. Of the 319 members of the kindred (six generations), 62 were found to have a hereditary nerve deafness varying greatly in severity.

3. A survey of the younger members of the kindred disclosed a number of individuals in whom high tone loss was present without conscious deafness. This is believed to represent an early form of the family deafness. Long term studies are necessary to establish this.

4. All but one of the edentulous members of the kindred were deaf. In addition, a high percentage of the examined members of the kindred had deviated septums, and many of these were deaf. The significance of these observations is not clear at the present time.

5. Tonsils, adenoids, allergy, malocclusion, and sinusitis apparently had no influence on the hereditary hearing impairment in this study.

6. The type of inheritance was found to be that of a dominant trait with complete penetrance.

7. The hypothesis is proposed that hereditary nerve deafness may represent a premature aging in the hearing mechanism.

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Sex-linked Nystagmus Associated with Red-green Color-blindness

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NYSTAGMUS, which may be defined as an involuntary to-and-fro movement of the eyes, occurs most frequently as a result of disease of the central nervous system or disturbance of the labyrinth. In these instances it consists of rhythmic, quick and slow components. It may also be a consequence of defective vision due to congenital cataracts, infantile macular lesions or albinism. This ocular type possesses a pendular movement, and lacks quick and slow components.

A special variety of nystagmus may be inherited. It resembles in appearance the ocular type; yet it is not associated with defective vision, for persons afflicted with it have an acuity of approximately 6/10 and could likely see 6/6 if only their eyes would stand still. The movements of the eyes are constant, horizontal and pendular, of small range on forward gaze and of increasing amplitude on gaze to the sides. The rate is about 120 beats per minute. In most cases it is noted by the mother when the child is a few weeks to a few months of age.

It happens that in southern Minnesota there are two large families, one not related to the other, in which nystagmus occurs as a sex-linked character. In one of these families, previously reported (Rucker, 1946), the character is entirely recessive in the female carriers. In the other family, the one to be reported herein, it is expressed in some of the female carriers and furthermore, in several of the members the nystagmus is associated with red-green color-blindness. This association, to my knowledge, has not been recorded previously. The relationship, however, is entirely fortuitous, for the only characteristics shared by the two conditions are that the faults within the central nervous system responsible for them are entirely unknown, and that both are carried on the X chromosome. (In some families hereditary nystagmus is transmitted on an autosome.)

REPORT OF PEDIGREE

Several of the members of the kindred to be reported herein were interested in their family tree and had preserved good records in note books and in family Bibles. Members of generation *I* (fig. 1) lived at the time of the American Revolution. The father of *I-5* is said to have participated in the Boston Tea Party, and her husband, *I-6*, served as a soldier in the Revolutionary War. Members of generation *II* were born about the year 1800.

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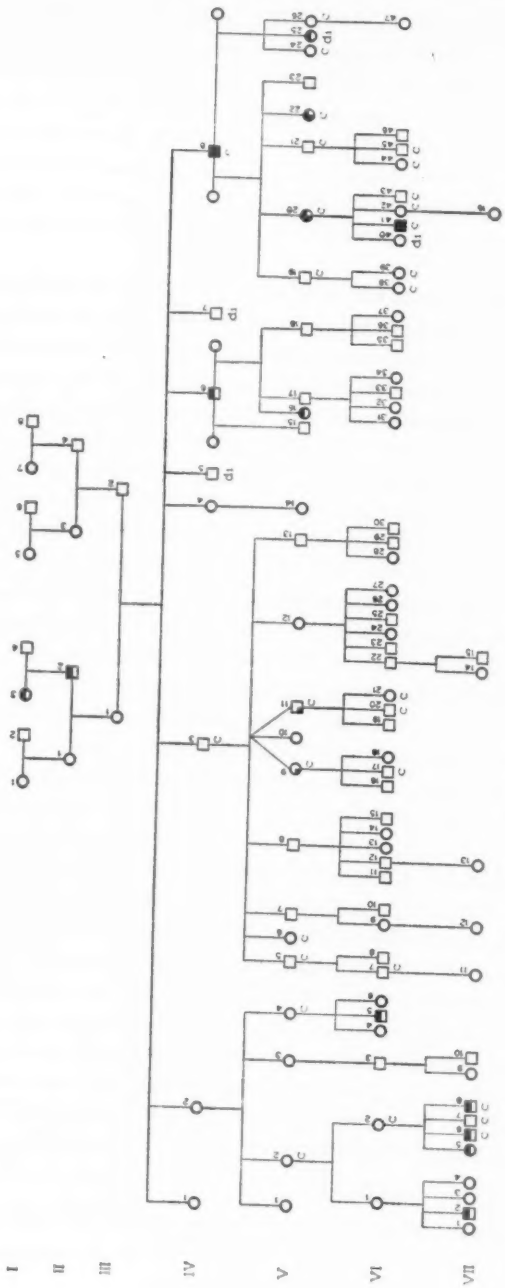

FIG. 1. Pedigree of family in which nystagmus is associated with red-green color-blindness.

Individual *1* of generation *III* lived from 1832 to 1921, and told tales of her parents and grandparents to her own grandchildren, one of whom kept a written record of this information which she has made available to me. Most of the members of generations *IV*, *V*, *VI* and *VII* have been examined by myself in calls made at their homes. Color vision was tested on the chart sold by the American Optical Company. Since the chart has been criticized as being inadequate for differentiating types of color-blindness, such an attempt was not made in this study. It does serve, however, as a guide to the completeness of the deficiency.

In generation *I*, individual *3* was afflicted with nystagmus, as was her son *II-2*. Although *III-1* was a carrier, several of her children and grandchildren who are still living are certain that she was not nystagmic. She transmitted the defect to two of her sons, *IV-6* and *IV-8*, and through her second daughter, *IV-2*, to several members in generations *VI* and *VII* by way of females in whom it was not expressed. *IV-3* has normal eyes, as have all of his descendants whom I have had the opportunity of examining except 2 of his triplets, who are partially red-green color-blind. This defect must have been derived from their mother, who is not a member of this kindred, and consequently it has no bearing on this study. *IV-6* and *V-16*, both of whom had nystagmus, are unfortunately no longer living. An examination of their eyes, especially their color sense, would have been of great interest.

IV-8, still living at the age of 77 years, is nystagmic and also is completely red-green color-blind. Three of his daughters were nystagmic, and the 2 who are living are incompletely red-green color-blind. Information is not available on the third. One of the living daughters, *V-22*, did not marry. The other, *V-20*, has a son, *VI-41*, who has nystagmus, and he, like his nystagmic grandfather, is completely red-green color-blind.

The manner is which the X chromosome of *IV-8* came to bear the gene both for nystagmus and for color-blindness I must leave for the professional geneticist to explain. In any event, in the descendants of *IV-8* this chromosome has remained intact, and these two characteristics have been transmitted together. In the affected males they are fully expressed; in the 2 nystagmic females who could be examined the color defect was incomplete. In *V-24* and *V-26* they must be present, but are recessive, for each of these women possesses a tainted X chromosome inherited from her father. Also demanding explanation is the absence of color-blindness in the nystagmic descendants of *IV-2*.

This pedigree is submitted with the hope that the editor or one of his associates will discuss the most plausible locations of the cross-overs.

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Estimation of Linkage in Rucker's Pedigree of Nystagmus and Colorblindness

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INTRODUCTION

ESTIMATION of linkage using all the information in a complicated pedigree is an onerous task. The problem has received little attention in the literature of genetics, Haldane being the principal contributor. In a series of papers dating from 1937, he has examined the problem of measuring the linkage intensity between two sex-linked genes, using for this purpose all of the published pedigrees showing both hemophilia and colorblindness. A recent paper by Haldane and Smith (1947) gives an extensive and detailed discussion of this particular problem, with attention to mutation and additional sources of the genes in question, and to several mathematical methods of estimation.

Rucker (1949) gives data bearing on another pair of sex-linked characteristics, namely colorblindness and nystagmus. His pedigree, apart from furnishing information on a new linkage in the human X chromosome, offers a new analytical complication. Both nystagmus and colorblindness are incompletely recessive in Rucker's pedigree, that is, they are sometimes expressed in heterozygous females. Although this phenomenon is known to occur in hemophilia, as well as colorblindness, examples of it were apparently not encountered in the pedigrees analysed by Haldane. The occurrence of such cases naturally complicates the estimation of the cross-over frequency, but also increases the information regarding this ratio.

When dominance of the normal sex-linked alleles is complete, only males supply appreciable information on linkage if at least one of the recessive genes is rare, for then doubly recessive females will be rare. It follows that the amount of information supplied by females varies with the degrees of dominance at the two loci, that is, with the probabilities that heterozygous females will be phenotypically recessive. Unless these probabilities, called penetrances, have been accurately ascertained by other studies, they must be estimated from the same pedigree for which linkage of the two genes is to be estimated, if the best possible estimate of linkage is desired. Furthermore, even if the penetrances were already known, they should be estimated from the pedigree at hand as a check on the identity of the genes and against various complications, e. g., epistasy.

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Theory of Estimation

Simultaneous estimation of all parameters, in this case a linkage and two penetrances, is theoretically desirable. Though adding to the algebraic and arithmetic labor, better estimates and better standard deviations of the estimates result. Also, measures of the relations between the several statistics, that is, their covariances or correlations, are found.

The classical solution of problems of estimation is the method of maximal likelihood (Fisher, 1922). It consists of choosing as estimates those values of the parameters which simultaneously maximize the probability of observing such data as have in fact been observed. The likelihood is defined as the logarithm of the probability of the data, excepting purely combinatorial factors. The maximal likelihood estimates are found by writing the likelihood as a function of the parameters, differentiating partially with respect to each, and finding the set of values of the parameters which makes the several derivatives vanish simultaneously. Inserting these estimates into the various second partial derivatives of the likelihood, the negatives of the amounts of information supplied by the data relative to the parameters are yielded. The matrix of amounts of information inverts to the covariance matrix, so that this method of estimation provides sampling variances and covariances for its estimates. This is obviously a valuable and inportant property. No other method of estimation seems preferable, especially for the simultaneous estimation of several parameters and the evaluation of their reliabilities. It will therefore be used to estimate linkage and penetrances from Rucker's pedigree.

Pruning the Genetic Tree

The first step in the solution of any problem of estimation is to rid the data of irrelevant items. This is of unusual importance in treating pedigrees because the task of writing the probability of the observed pedigree is sufficiently complicated without involving individuals who contribute no information bearing on the parameters being estimated. Inspection of Rucker's pedigree reveals that many individuals are irrelevant to the estimation of linkage between nystagmus and colorblindness, and to the estimation of either of the penetrances.

All descendants of unaffected males may be ignored because neither recessive gene is transmitted. If colorblindness has been introduced among the progeny of such a male, it may be caused by a distinct allele (or even by a gene at another locus) from that affecting *IV-8* and, presumably, his descendants. Hence such colorblindness, shown by *V-9* and *V-11*, is likely to be irrelevant and even misleading in estimating the penetrance of the particular gene which made *IV-8* colorblind. With an exception to be noted immediately, male progeny of affected males are always uninformative, unless they happen also to be sons of affected or possibly affected females. Therefore, the descend-

ants of *IV-3*, of *VI-3*, and of *IV-6*, excepting *V-16*, may be disregarded. The exception is that sons of affected males are informative regarding the introduction of colorblindness into the pedigree, provided their color vision has been tested. Therefore, though *V-23* contributes nothing, his brothers *V-19* and *V-21* must be retained for the information they provide concerning the probability that their mother was heterozygous for colorblindness. Also, nystagmus obviously entered the pedigree through *III-1* (unless mutations be assumed), *III-2* being unaffected. Hence only *I-3*, *II-2* and *III-1* of the first three generations need be retained.

Any others who have not been tested for colorblindness, and who give no information regarding the penetrance of nystagmus, may be ignored. This eliminates *IV-5* and *IV-7*, but not *VI-40* if the nystagmic condition can be

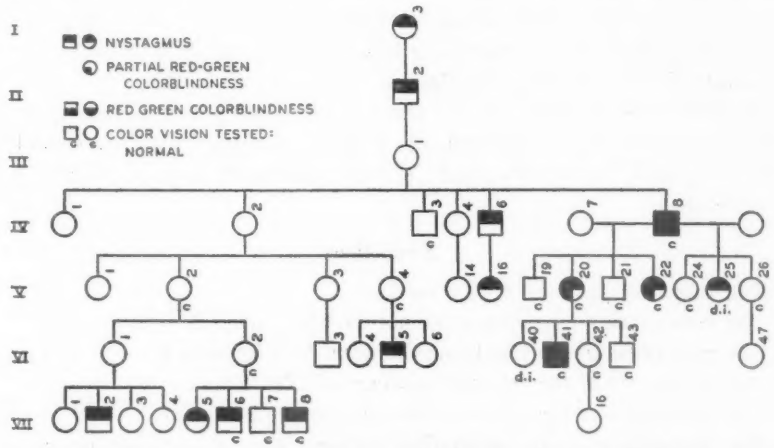

FIG. 1. Pedigree of sex-linked nystagmus and colorblindness, abbreviated from Rucker to show only those members supplying information on one or more of the parameters x, p, r and f.

recognized sufficiently early in infancy. Making this assumption, *VI-40* has been retained. The reduced pedigree is given in figure 1, using Rucker's symbols.

Simplifying Assumptions

The second step should be to consider what simplifying assumptions may be made with little sacrifice of information and little bias to the estimates. Haldane has shown that additional sources of rare genes need not be considered in estimating linkage, unless they provide an alternative explanation of apparent recombinations. In such cases the importance of considering additional sources is greatest when linkage is close. No such case occurs in Rucker's pedigree, nor is linkage very close. Similarly, it is obvious that consideration of additional sources can shed little light on the penetrance of rare genes, but

give an amount of information which increases with the population frequency of the gene. It is assumed here that nystagmus is so rare that additional sources may be neglected. This assumption is not made for colorblindness.

Mutation may also explain apparent recombinations. In fact, a single mutation, to colorblindness in *IV-8*, would seriously reduce the amount of information regarding linkage, nearly confining such information to the progeny of *IV-8*. However, there appears to be no reason to suppose that colorblindness is (or has been) seriously detrimental to survival value. Therefore it is reasonable to assume that the probability that any particular gene for colorblindness is the result of a mutation is small enough to be ignored.

There may be an appreciable force of selection acting against nystagmus, and hence there may be an appreciable probability that a particular gene for nystagmus is itself the result of mutation. However, Haldane and Smith show that, even for a gene subject to very great selection pressure, the effect of including mutation in estimating linkage is very slight, and mutation will be ignored in the following calculations.

Additional assumptions are (1) there is no crossing over in males, (2) somatic mutation may be ignored, (3) females homozygous for colorblindness are "completely" colorblind, and (4) both nystagmus and colorblindness are sex-linked.

Symbolism

The following symbols will be used:

n, the gene causing nystagmus, the normal allele being **N**

b, the gene causing colorblindness, the normal allele being **B**

p, the penetrance of the gene for nystagmus in **Nn** females

r, the penetrance of the gene for colorblindness in **Bb** females

χ, the probability of recombination between the loci of nystagmus and colorblindness

f, the frequency of the gene for colorblindness relative to all genes occurring at that locus

$q = 1 - p$

$s = 1 - r$

$g = 1 - f$

$x = \frac{1}{2}\chi$

$y = \frac{1}{2}(1 - \chi)$, and note $x + y = \frac{1}{2}$.

THE PROBABILITY OF THE OBSERVED PEDIGREE

The task of writing the probability of the observed pedigree will now be begun. It should be remarked at the outset that the form of the pedigree is accepted, including the sexes of the various individuals and their relationships,

and the problem is to calculate the probability of the observed phenotypes as a function of the several parameters to be estimated. The rejection of mutation implies the assumption that *III-1* is doubly heterozygous. The probability of the whole pedigree will consist of two terms, one for *III-1* in coupling and one for repulsion. On the data supplied concerning the ancestors of *III-1*, coupling and repulsion are equally likely, because the gene for colorblindness could have come as well from one parent as from the other.

Consider first the probability of *IV-8* and his progeny when *III-1* is in coupling. The probability of *IV-8* himself is simply y. His offspring are divided into two sibships which must be considered separately. For *V-19*, *20*, *21* and *22*, the mother may have been **BB** or **Bb**, with probabilities g^2 and $2fg$, respectively, but she could not have been **bb** because her two tested sons have normal color vision. The probability of the sibship is therefore $p^2(g^2r^2 + fgr^2/8)$ or $p^2r^2g(1 + 7g)/8$. And similarly, for *V-24*, *25*, and *26*, the probability is $pq^2s^2(g^2+fg/2)$ or $pq^2s^2g(1 + g)/2$. For each of *VI-40* and *VI-47* the probability is $\frac{1}{2}(1 + q)$, the first term corresponding to the transmission of **N**, the second to the transmission but non-appearance of **n**. For *VI-41* and *43* the probabilities are each y.

For *VI-42* the situation is more complicated. There is probability y that she received **nb** from *V-20* and qs that neither gene showed itself, g that she received **B** from her father, and $\frac{1}{2}(1 + q)$ that *VII-16* should not be nystagmic, combining to $\frac{1}{2}yqsg(1 + q)$. In addition, there is probability y that *VI-42* received **NB** from *V-20*, in which case *VII-16* gives no information on the penetrance of **n**, and probability fs that *VI-42* received **b** from her father but was unaffected, and g that her father transmitted **B**, combining to $y(g + fs)$. Also, she may have received **Nb** with probability x, requiring **B** from her father with probability g, combining to xgs. Lastly, she may have received **nB** with probability x, either **B** or **b** from her father, and *VII-16* may have received either **N** or **n**, combining to $\frac{1}{2}xq(g+fs)(1+q)$. Accumulation of these possibilities yields $xgs + y(g+fs) + \frac{1}{2}x(g+fs)q(1+q) + \frac{1}{2}ysgq(1+q)$, the total probability of *VI-42* and *VII-16* if *III-1* is in coupling.

This will suffice for illustration of the method of finding probabilities of individuals and small groups. It should be particularly noted, however, that, when there is more than a single possible genotype for any individual, it is usually necessary to write the probability of that individual and all his progeny separately for each possible genotype, as for *VI-42* and *VII-16* above, though there are exceptions to this rule. For example, *IV-2* may be of several different genotypes, but she must be **Nn** because **n** appears in her progeny and mutation has been assumed rare enough to be ignored. Therefore she is of a single definite genotype with respect to nystagmus. It follows that the probabilities of *V-1*, *V-3*, *VI-3*, and, by a similar argument, those for *VI-1*, *4*, *5*,

and *6*, and *VII-1*, *2*, *3*, *4*, and *5*, will be the same for each of the possible genotypes of *IV-2*, and may be calculated without regard to the genotype of *IV-2*.

The following list gives the probabilities of observing various individuals and small groups, all for *III-1* in coupling:

Individual(s)	*Probability*
I-3	p
II-2	$\frac{1}{4}$
III-1	qfg
IV-1	$(1 + q)/2$
IV-3	y
IV-4; V-14	$(2 + q + q^2)/4$
IV-6; V-16	$p/2$
IV-8	y
V-1	$(1 + q)/2$
V-3; VI-3	$(2 + q)/4$
V-19, 20, 21, 22	$p^2r^2g(1 + 7g)/8$
V-24, 25, 26; VI-47	$pq^2(1 + q)s^2g(1 + g)/4$
VI-1; VII-1, 2, 3, 4	$q(1 + q)^2/32$
VI-4, 5, 6	$(1 + q)^2/8$
VI-40, 41, 43	$y^2(1 + q)/2$
VI-42; VII-16	$xgs + y(g + fs) + x(g + fs)q(1 + q)/2 + ysgq(1 + q)/2$
VII-5	$p/2$

The final entry in this list, for *IV-2; V-2, 4; VI-2; VII-6*, *7*, and *8*, is found, after some simplification, to be

$$xygq^4[ygs(x + ys)(xy^2s + g/8) + \tfrac{1}{2}g(x + ys)(xy^2fs + g/8) + xyfs^2(x^2gs + xy^2fs + g/8)]$$
$$+ \tfrac{1}{4}xgq^4[\tfrac{1}{2}g(xy^2fs + g/8) + xyfs^2(x^2gs + xy^2fs + g/8)] + \tfrac{1}{4}xyfgq^4s^2(xy^2s + g/8)$$
$$+xfq^4[\tfrac{1}{2}yg(y + xs)(xy^2fs + g/8) + x^2gs(y + xs)(xy^2s + g/8) + y^2fs^2(x^2gs + xy^2fs + g/8).$$

Of these four terms, the first and third correspond to no recombination in forming the gamete which *III-1* passed to *IV-2*, the second and fourth resulting if there is recombination. The product of all the listed probabilities is the probability of the whole pedigree on the assumption that *III-1* was in coupling.

If *III-1* is in repulsion, only the probabilities for *IV-2*, *3* and *8* are altered, and only by interchanging x and y. That is, the probability of *IV-2*, *3* and *8*, with *III-1* in coupling, contains y^3 or xy^2 accordingly as *IV-2* is supposed to be in coupling or repulsion. If *III-1* is in repulsion, these factors become x^3 and x^2y, respectively. Hence the two terms of the total probability of the observed pedigree, one for coupling and one for repulsion in *III-1*, may be combined for the four possible genotypes of *IV-2*. Non-recombination genotypes of *IV-2* combine to give a term involving $x^3 + y^3$, recombination types to give one involving $x^2y + xy^2$, the latter reducing to $\frac{1}{2}xy$, since $x + y = \frac{1}{2}$. The probability of the whole pedigree, again after some simplification, is therefore

$P = 2^{-23}p^6q^3(1+q)^3(2+q)(2+q+q^2)r^2s^2fg^3(1+g)(1+7g)xy^2AB,$
where $A = yg + yfs + xgs + \frac{1}{2}q(1+q)(xg + xfs + ygs),$
and $B = g(x^3+y^3)[g(x+ys)(ysD+\frac{1}{2}E) + xyfs^2F]$
$+ gy(\frac{1}{2}gE + yfs^2F)/8 + fgs^2(x^3+y^3)D/4$
$+ fy[g(y+xs)(x^2sD+\frac{1}{2}yE) + y^3fs^2F],$
with $D = xy^2s + g/8,$
$E = xy^2fs + g/8,$
$F = x^3gs + xy^2fs + g/8.$

It should be remembered that this expression is approximate because of various assumptions. For example, if it were desirable to take explicit account of the possibility of mutation to colorblindness in *IV-8*, the above expression would be multiplied by $(1 - m)$, and there would be an additional term $\frac{1}{4}mp^3q^2(1+q)^2r^2s^2y^2g^4A$, where m is the probability of mutation of **B** to **b**, for which a value would have to be adopted or estimated from the data at hand. For any small value of m, such as 0.0001 or 0.00001, it is plain that including mutation can barely affect the estimates.

EVALUATION OF THE ESTIMATES

The purely algebraic and arithmetic task of ascertaining what values of the parameters simultaneously maximize P is considerable. It can best be approached by ignoring additional sources of colorblindness while getting provisional estimates of the parameters, taking account later of the effect of such additional sources to modify those estimates. This amounts to putting unity for g and zero for f (except that f which corresponds to the "original" source of **b**), resulting in the following much simplified expression:

$P_0 = 2^{-19}p^6q^3(1+q)^3(2+q)(2+q+q^2)r^2s^2xy^2A_0B_0,$
where $A_0 = y + xs + \frac{1}{2}q(1+q)(x+ys),$
and $B_0 = (x^3+y^3)(x+ys)\,[ys(xy^2s + 1/8) + 1/16] + y/128.$

It follows that the likelihood, L_0 (the natural logarithm of P_0 except for the irrelevant constant 2^{-19}) is

$$L_0 = 6\log p + 8\log q + 9\log(1+q) + \log(2+q) + \log(2+q+q^2) + 2\log r + 2\log s + \log x + 2\log y + \log A_0 + \log B_0.$$

Differentiating partially with respect to each of the three parameters,

$$\frac{\partial L_0}{\partial p} = \frac{6}{p} - \frac{8}{q} - \frac{9}{1+q} - \frac{1}{2+q} - \frac{1+2q}{2+q+q^2} + \frac{1}{A_0}\frac{\partial A_0}{\partial p},$$

$$\frac{\partial L_0}{\partial r} = \frac{2}{r} - \frac{2}{s} + \frac{1}{A_0}\frac{\partial A_0}{\partial r} + \frac{1}{B_0}\frac{\partial B_0}{\partial r},$$

$$\frac{\partial L_0}{\partial x} = \frac{1}{x} - \frac{2}{y} + \frac{1}{A_0}\frac{\partial A_0}{\partial x} + \frac{1}{B_0}\frac{\partial B_0}{\partial x},$$

where

$$\frac{\partial A_0}{\partial p} = -\tfrac{1}{2}(x + ys)(1 + 2q), \qquad \frac{\partial A_0}{\partial r} = -x - \tfrac{1}{2}yq(1 + q),$$

$$\frac{\partial A_0}{\partial x} = -\tfrac{1}{2}r\,(2-q-q^2),$$

$$\frac{\partial B_0}{\partial p} = 0,$$

$$\frac{\partial B_0}{\partial r} = -y(x^3 + y^3)[(x + 2ys)(xy^2s + \tfrac{1}{8}) + sxy^2(x + ys) + \tfrac{1}{16}],$$

and

$$\frac{\partial B_0}{\partial x} = 3(x - y)(x + ys)[ys(xy^2s + 1/8) + 1/16]/2 + r(x^3 + y^3)[ys(xy^2s + 1/8) + 1/16] + (x^3 + y^3)(x + ys)(s^2y^3 - 3s^2xy^2 - s/8) - 1/128.$$

It is not difficult to find values of p, r, and x, which make the three partial derivatives of L_0 simultaneously equal zero. Obviously, the terms involving A_0 and B_0 will change slowly compared to such terms as the reciprocals of p, q, r, s, x, and y. Therefore, rough estimates may be found using only the first two terms of the right members of the three partial derivatives. Approximately, $p_0 = 6/14$, $r_0 = 1/2$, and $x_0 = 1/6$. Furthermore, these are easily seen to be over-estimates. It will be convenient to adopt 0.3, 0.4, and 0.1, as first values of p_0, r_0, and x_0, respectively, and to calculate the corresponding values of the three partial derivatives of L_0. The following values are found:

$A_0 = 0.6623$	$B_0 = 0.005220$	
$\frac{\partial A_0}{\partial p} = -0.408$	$\frac{\partial B_0}{\partial p} = 0$	$\frac{\partial L_0}{\partial p} = 1.5385$
$\frac{\partial A_0}{\partial r} = -0.338$	$\frac{\partial B_0}{\partial r} = -0.003740$	$\frac{\partial L_0}{\partial r} = 0.4400$
$\frac{\partial A_0}{\partial x} = -0.162$	$\frac{\partial B_0}{\partial x} = -0.021383$	$\frac{\partial L_0}{\partial x} = 0.6592$

Approximate second derivatives may easily be found, omitting the term $(1+2q)/(2+q+q^2)$ and terms involving A_0 and B_0. They are -86.25, -18.06, and -112.50, for p, r, and x, respectively. Adjustments to the adopted first values of p_0, r_0, and x_0, are found by dividing the first derivatives by the corresponding second derivatives and changing the signs of the quotients. Applying these adjustments, the improved values are 0.318, 0.424, and 0.106. The

corresponding values of the first derivatives are 0.0536, 0.0396, and 0.0563, markedly nearer to zero in each case, and suggesting further adjustments of only 0.0006, 0.0022, and 0.0005.

The proper value of f, the frequency of **n** in the population of **N** and **n** genes, and its effect on the estimates of p, r, and x, may now be examined. A value sometimes given for f is 0.08, but this appears to be the total for all loci and all alleles which cause defective color vision, and Haldane and Smith took f to be only 0.014 for deuteranopia. However, so long as it is small, variations in the value of f have little effect on the estimates of p, r, and x. In fact, adopting 0.1 as the value of f, and again using 0.318, 0.424, and 0.106 for p, r and x, a tiresome calculation finds the derivatives of L to be 0.0680, −0.1067, and −0.0537. Hence the needed adjustments to the provisional values of p, r, and x are 0.0008, − 0.0059, and − 0.0005 − . Before applying these adjustments, the information matrix will be calculated.

EVALUATION OF THE INFORMATION MATRIX

This requires evaluation of the six second partial derivatives of L_0, which are

$$\frac{\partial^2 L_0}{\partial p^2} = -\frac{6}{p^2} - \frac{8}{q^2} - \frac{9}{(1+q)^2} - \frac{1}{(2+q)^2} + \frac{3-2q-2q^2}{(2+q+q^2)^2} - \frac{1}{A_0^2}\left(\frac{\partial A_0}{\partial p}\right)^2 + \frac{1}{A_0}\frac{\partial^2 A_0}{\partial p^2},$$

$$\frac{\partial^2 L_0}{\partial r^2} = -\frac{2}{r^2} - \frac{2}{s^2} - \frac{1}{A_0^2}\left(\frac{\partial A_0}{\partial r}\right)^2 + \frac{1}{A_0}\frac{\partial^2 A_0}{\partial r^2} - \frac{1}{B_0^2}\left(\frac{\partial B_0}{\partial r}\right)^2 + \frac{1}{B_0}\frac{\partial^2 B_0}{\partial r^2},$$

$$\frac{\partial^2 L_0}{\partial x^2} = -\frac{1}{x^2} - \frac{2}{y^2} - \frac{1}{A_0^2}\left(\frac{\partial A_0}{\partial x}\right)^2 + \frac{1}{A_0}\frac{\partial^2 A_0}{\partial x^2} - \frac{1}{B_0^2}\left(\frac{\partial B_0}{\partial x}\right)^2 + \frac{1}{B_0}\frac{\partial^2 B_0}{\partial x^2},$$

$$\frac{\partial^2 L_0}{\partial p \partial r} = -\frac{1}{A_0^2}\frac{\partial A_0}{\partial p}\frac{\partial A_0}{\partial r} + \frac{1}{A_0}\frac{\partial^2 A_0}{\partial p \partial r},$$

$$\frac{\partial^2 L_0}{\partial p \partial x} = -\frac{1}{A_0^2}\frac{\partial A_0}{\partial p}\frac{\partial A_0}{\partial x} + \frac{1}{A_0}\frac{\partial^2 A_0}{\partial p \partial x}$$

$$\frac{\partial^2 L_0}{\partial r \partial x} = -\frac{1}{A_0^2}\frac{\partial A_0}{\partial r}\frac{\partial A_0}{\partial x} + \frac{1}{A_0}\frac{\partial^2 A_0}{\partial r \partial x} - \frac{1}{B_0^2}\frac{\partial B_0}{\partial r}\frac{\partial B_0}{\partial x} + \frac{1}{B_0}\frac{\partial^2 B_0}{\partial r \partial x}.$$

Also needed are

$$\frac{\partial^2 A_0}{\partial p^2} = x + ys, \qquad \frac{\partial^2 A_0}{\partial r^2} = 0, \qquad \frac{\partial^2 A_0}{\partial x^2} = 0,$$

$$\frac{\partial^2 A_0}{\partial p \partial r} = \tfrac{1}{2}y(1+2q), \qquad \frac{\partial^2 A_0}{\partial p \partial x} = -\tfrac{1}{2}r(1+2q), \qquad \frac{\partial^2 A_0}{\partial r \partial x} = -1 + \tfrac{1}{2}q(1+q),$$

and

$$\frac{\partial^2 B_0}{\partial r^2} = y^2(x^3 + y^3)[xy(2x + 3ys) + 3sxy^2 + 1/4],$$

$$\frac{\partial^2 B_0}{\partial x^2} = [3(x + ys) - 3r(y - x)][ys(xy^2s + 1/8) + 1/16]$$
$$- 6y(y - x)s^2(x + ys)(x^3 + y^3)$$
$$+ s[sy^2(y - 3x) - 1/8][2r(x^3 + y^3) - 3(y - x)(x + ys)],$$

$$\frac{\partial^2 B_0}{\partial r\,\partial x} = [(x^3 + y^3) - \tfrac{3}{2}y(x - y)][(x + 2ys)(xy^2s + 1/8) + sxy^2(x + ys) + 1/16]$$
$$- y(x^3 + y^3)[(r - s)(xy^2s + 1/8) + (2x + 3ys)sy(y - 2x) + rsxy^2].$$

The negatives of the second partial derivatives, evaluated at the estimated values of the parameters, are the informations with respect to the three parameters for which L_0 has been differentiated. They are 79.60, 17.29, 104.14, −0.41, 0.95, and −2.86, in the order in which the derivatives were listed above, and the information matrix is

$$I = \begin{array}{c} \begin{matrix} p & r & x \end{matrix} \\ \begin{Bmatrix} 79.60 & -0.41 & 0.95 \\ -0.41 & 17.29 & -2.86 \\ 0.95 & -2.86 & 104.14 \end{Bmatrix} \begin{matrix} p \\ r \\ x \end{matrix} \end{array}$$

Inverting by any convenient method, such as that illustrated by Stevens (1938), the covariance matrix is found to be

$$V = \begin{array}{c} \begin{matrix} p & r & x \end{matrix} \\ \begin{Bmatrix} 0.01257 & 0.00028 & -0.00011 \\ 0.00028 & 0.05811 & 0.00159 \\ -0.00011 & 0.00159 & 0.00965 \end{Bmatrix} \begin{matrix} p \\ r \\ x \end{matrix} \end{array}$$

and the terms of the leading diagonal are the variances of the estimates of p_0, r_0, and x_0.

THE ESTIMATES OF LINKAGE AND PENETRANCE

The estimates derived from P_0, (that is, from taking f to be zero), and their standard deviations, are

$$p_0 = 0.319 \pm 0.112$$
$$r_0 = 0.426 \pm 0.241$$
$$x_0 = 0.1065 \pm 0.098$$

and, with $\chi = 2x$, $\qquad \chi_0 = 0.213 \pm 0.196$

This calculation can be repeated, with much labor, using 0.1 for f. The estimates of p, r, and x, and their standard deviations, are

$$p = 0.319 \pm 0.112$$
$$r = 0.418 \pm 0.241$$
$$x = 0.1055 \pm 0.098.$$

The only change, to three decimals, occurs in the estimate of r, amounting to less than four hundredths of its standard deviation. This illustrates the small importance of the correct value of f.

DISCUSSION OF THE ESTIMATES

The penetrance of nystagmus, 0.319 ± 0.112, is moderately well established, being unlikely to be below 0.1 or above 0.5. The penetrance of color-blindness is much less well established, and there is doubt as to exactly which loci and which alleles have been allowed to contribute to this estimate, because of imperfections in the method of testing color vision.

Linkage of the two genes was, of course, implied by the assumption of sex-linked transmission of both abnormalities, and the estimated cross-over proportion, 0.213 ± 0.196, deviates from 0.5 in the direction favoring this supposition. However, the present data are inadequate to establish the deviation as significant. At any rate, an estimate and its standard deviation have been found, and this is now available for easy combination with estimates from additional data as they become available.

It is worth specific mention that the estimates of p, r, and x, are nearly independent. It is easy to see that this is to be expected, for half the children of doubly heterozygous females will be males, and hence will yield information regarding the frequency of crossing-over unaffected by the values of the two penetrances. The covariances of the estimates of p and r, p and x, and r and x, are only 0.00026, -0.00012, and 0.00124, the correlations being 0.010, -0.011, and 0.052. This explains the success of the method used above for calculating improvements to the adopted values of p, r, and x, which used only three of the six second derivatives. In fact, whenever $\partial^2 L/\partial\alpha\partial\beta$ is of the same order of magnitude as the square root of the product of $\partial^2 L/\partial\alpha^2$ and $\partial^2 L/\partial\beta^2$, a more sophisticated calculation of adjustments is usually worth while.

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Rh-Incompatibility and Mental Deficiency

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THAT the Rh factor is correlated with hemolytic disease of the new-born may be considered an established fact, based upon clinical, serological and genetical observations. It is known that signs and symptoms of cerebral damage are not uncommon in children affected with hemolytic disease. Histologically, the cerebral lesion is most distinctly manifest in the form of a so-called kernicterus. The clinical pictures presented by some of these patients exhibit disturbances of mainly extrapyramidal character and sometimes feeble-mindedness.

It seems reasonable to assume that cerebral lesions of this type may appear also in cases where no obvious symptoms of hemolytic disease have been found in the early history. Potter (1947) writes: "The 16 infants in our series in whom kernicterus was demonstrated on post-mortem examination exhibited two distinct clinical patterns. In 6, hemolytic disease was severe at the time of birth and became progressively worse in the next few hours; in 10, the symptoms were mild, death was usually unexpected, and histological changes in the organs were minimal." A child who does not show any symptoms of hemolytic disease during neonatal life may therefore later possibly show sequelae in which mental defectiveness is the predominant symptom.

If this mechanism responsible for feeble-mindedness is of general significance and not a rarity, we might expect a surplus of Rh-negative mothers of patients suffering from mental deficiency of hitherto unknown etiology. Such surpluses have actually been claimed by several authors (Yannet & Lieberman 1944, 1945, 1946; Snyder, Schonfeld & Offerman 1945*a*,*b*; Snyder, 1946).

The evidence hitherto published is, however, not very convincing. The results have been doubted by Wiener (1946) and criticized by Cappell (1947).

THE PROBLEM

In the present paper the following two main questions will be considered:

1. Is it possible to show statistically that Rh-incompatibility is of practical importance as an etiological factor in undifferentiated mental deficiency?

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2. What is the frequency of encephalopathies due to Rh-incompatibility in a population of mental defectives?

MATERIAL

The patients of three institutions for mental defectives have been examined:

1. The Vipeholm Hospital, which is a State mental hospital for uneducable mental defectives, mainly male adults. Most patients here are difficult to manage owing to extreme helplessness, uncleanliness, and disorderly conduct. The hospital admits patients from all parts of the country.

2. The Möllevångshemmet, a training school for educable feeble-minded children between 8 and 18 years of age. This home admits patients from the south of Sweden only.

3. The Nyhem asylum. Most patients here belong to the same category as the inmates of Vipeholm Hospital, whilst a small number are educable. Admittance is from the south of Sweden only.

The total number of patients and sex incidence will be apparent from table 1.

TABLE 1. THE SEX DISTRIBUTION OF THE PRESENT MATERIAL

HOSPITAL	MALE	FEMALE	TOTAL
Vipeholm	678	0	678
Möllevångshemmet	54	75	129
Nyhem	91	79	170
Total	823	159	977

SEROLOGICAL TECHNIQUE

Blood specimens were obtained by venipuncture. In every case blood group determinations were made within 48 hours of taking the sample. The A-B-O groups were determined by examinations not only of the cells but also of the serum. The Rh-examinations were carried out by means of human anti-Rh serum with the specificity of anti-Rh_0 (anti-D). Every blood specimen was examined with at least two anti-Rh_0 sera. Tests for antibodies were made in the following media: normal saline, normal human serum, and bovine albumin.

THE BLOOD GROUP DISTRIBUTION IN THE PRESENT MATERIAL

The blood group of each of the 977 patients was determined. A comparison of the distribution of the A-B-O and Rh-groups of the present material and that of the normal Swedish population is shown in tables 2a and 3a. Furthermore, the distribution in a group of patients initially classified as "undifferentiated mental deficiency of unknown etiology" was studied. This group consisted of patients remaining after the exclusion of cases belonging to

groups 1 to 4 (see below, p. 69). The blood group distribution in this undifferentiated group is shown in tables 2b and 3b.

The blood group distribution of the total material and that of the undifferentiated group were quite normal. No statistical differences were found when compared with the normal population. If Rh-incompatibility were an essential cause of undifferentiated mental deficiency, a surplus of Rh-positive individuals would be expected among these patients, as nearly 100 per cent of individuals affected with hemolytic disease are Rh-positive. However, it is evident that Rh-positiveness is not a sensitive indicator. If 10 per cent of all

TABLE 2

The distribution of A-B-O blood groups in (a) the total material and (b) the group of mental defectives classified as "undifferentiated feeblemindedness", compared with normal Swedish material (Wolff, 1946: 2000 men and 2000 women; O = 37.725, A = 47.350, B = 10.050 and AB = 4.875 per cent).

(a)

BLOOD GROUP	OBSERVED o	CALCULATED c	$o - c$	$(o - c)^2/c$
O	388	368.6	+19.4	1.0
A	446	462.6	−16.6	0.6
B	90	98.2	−8.2	0.7
AB	53	47.6	+5.4	0.6
Total.....	977	977.0	0.0	2.9

$\chi^2 = 2.9$, D.F. = 3, $0.5 > P > 0.3$.

(b)

BLOOD GROUP	o	c	$o - c$	$(o - c)^2/c$
O	264	248.2	+15.8	1.0
A	299	311.6	−12.6	0.5
B	60	66.1	−6.1	0.6
AB	35	32.1	+2.9	0.3
Total.....	658	658.0	0.0	2.4

$\chi^2 = 2.4$, D.F. = 3, $0.5 > P > 0.3$.

mental deficiency were caused by Rh-incompatibility, the expected figure of Rh-positives would be 85.6 per cent. This figure would then have to be compared with the 84 per cent of the normal material. A very large sample would evidently be necessary to establish the statistical significance of such a difference. This preliminary calculation only permits the conclusion that more than 75 per cent of all mental deficiency is caused by factors other than Rh-incompatibility.

In order to obtain a figure more sensitive to fluctuations, a further number of patients without apparent signs or symptoms referable to hemolytic dis-

ease had to be excluded from those belonging to the above mentioned undifferentiated group. Furthermore, the mothers had to be examined serologically. Those patients in our material who could be assigned to one of the groups mentioned below have been excluded:

1. *Hereditary forms:*

a. Mental deficiency, when found in the ascendancy or descendancy, or when there is consanguinity between the parents and other affected persons in the pedigree. Cases with only mentally deficient sibs have not been excluded, as hemolytic disease has a familial character.

b. Phenylpyruvic oligophrenia

c. Epiloia

TABLE 3

The distribution of the Rh blood groups in (a) the total material and (b) the group of mental defectives classified as "undifferentiated feeblemindedness", compared with normal Swedish population (Wolff).

(a)

	Rh+	Rh−	n
Mental defectives of the total material	821 (84.2%)	156 (15.8%)	977
Normal Swedish population. (Wolff, 1946)	1088 (84.0%)	208 (16.0%)	

$\chi^2 = 0.0$, D.F. = 1

(b)

BLOOD GROUP	o	c	$o - c$	$(o - c)^2/c$
Rh+	558	552.7	+5.3	0.1
Rh−	100	105.3	−5.3	0.3

$\chi^2 = 0.4$, D.F. = 1, $0.7 > P > 0.5$

2. *Secondary forms:*

a. Encephalitides and encephalomeningitides

b. Birth traumas

c. Nuclear jaundice. Obvious cases of nuclear jaundice in combination with mental deficiency should not be classified as undifferentiated mental deficiency of unknown etiology. As pointed out by Cappell (1947), they should therefore be excluded.

3. *Mongolian idiots*

4. *Cases with dementia owing to:*

a. Schizophrenia

b. Cryptogenous epilepsy

5. *All Rh-negative patients*

6. *All patients who are first-born.* It is a rare exception for the first child to be affected with hemolytic disease.

Furthermore, it should be mentioned that as it is known that such symptoms could be found in hemolytic disease (Potter, 1947) a few cases with spastic diplegia of unknown etiology have not been excluded.

After these exclusions there remains a group of mental defectives who satisfy the following criteria:

i Unknown etiology,
ii Undifferentiated clinical picture,
iii Rh-positive,
iv Born as number two or later in the sibship.

The mothers of patients belonging to this group have been traced in the Church Register. In several cases the mother was no longer living. It was possible to trace the addresses of 115 mothers. Of these, 25, mainly resident in Scania, were visited by us personally. From 76 other mothers, scattered all over the country, blood specimens were obtained by the courtesy of district physicians and district nurses. Thus, altogether, 101 mothers were examined serologically.

TABLE 4

Distribution of Rh blood groups among mothers of Rh-positive mental defectives of unknown etiology. (Selected material as described in the text).

MOTHERS	OBSERVED o	CALCULATED e	$o - e$	$(o - e)^2/e$
Rh-positive	86	85.0	1.0	0.01
Rh-negative	15	16.0	−1.0	0.06
	101	101.0	0.0	0.07

$\chi^2 = 0.07$, D.F. $= 1, 0.9 > P > 0.8$

RESULTS

The main interest is now centered upon the 101 Rh-positive mental defectives and their mothers, selected in the manner described above. For this group the following theoretical question must be answered. If we select a number of Rh-positive individuals from the general population, what will be the frequency of Rh-negative individuals among their mothers? Suppose the frequencies of the genes **rh** and **Rh** are p and q, respectively. The probability of any mother being **rh rh** is p^2. The probability that her child will receive the **Rh** gene from the father is q, this being the proportion of gametes carrying **Rh**. Hence, the probability of an Rh-negative mother with Rh-positive child is p^2q, and this, divided by the proportion of Rh-positive individuals $(1 - p^2)$, gives the expected proportion of Rh-negative mothers among mothers of Rh-positive patients. This proportion may also be written as $p^2/(1 + p)$. According to Wolff (1946), the frequencies of Rh-positive and Rh-negative individuals in the normal Swedish population are 83.95 and 16.05 per cent, respectively. Using these figures, the answer to the above-mentioned question

is found to be 11.4 per cent. Among the 101 mothers 15 were Rh-negative. As will be apparent from table 4, there is no statistical difference between the

TABLE 5. COMPARISON OF OBSERVED AND EXPECTED A-B-O BLOOD GROUP FREQUENCIES AMONG 101 MOTHER-CHILD PAIRS

This group comprises cases of "undifferentiated" feeblemindedness, selected as described is the text. The expected frequencies are calculated from gene frequencies found in the general Swedish population (Wolff, 1946): $p = 0.31$ (gene A), $q = 0.08$ (gene B), $r = 0.61$ (gene O).

MOTHER-CHILD PAIR	PROBABILITY P	EXPECTED FREQUENCY $c = 101 \times P$	OBSERVED FREQUENCY o	$(o - c)^2/c$
*Mother O Patient A	pr^2	11.7	14	0.45
*Mother B Patient A	pqr	1.5	2	
*Mother B Patient AB	$pq(q + r)$	1.7	2	
*Mother O Patient B	qr^2	3.0	3	
*Mother A Patient B	pqr	1.5	0	
*Mother A Patient AB	$pq(p + r)$	2.3	3	
‡Mother A Patient O	pr^2	11.7	6	2.8
‡Mother AB Patient B	$pq(q + r)$	1.7	2	
‡Mother B Patient O	qr^2	3.0	2	
‡Mother AB Patient A	$pq(p + r)$	2.3	2	
Heterospecific Pairs (total of above)		38.8	36	0.33
Homospecific Pairs		62.2	65	
Total		101.0	101	

* "Incompatible" pairs in which A or B antigen is present in child but absent in mother.
‡ Heterospecific pairs in which A or B antigen is present in mother but absent in child.

observed figures and those calculated. We have thus not been able to confirm the previous results of Yannet and Liebermann, and Snyder and co-workers, as published in their communications cited above.

In all of the 15 Rh-negative mothers tests for anti-Rh antibodies were negative. No evidence of neonatal jaundice of any of those 15 patients with a Rh-negative mother could be traced, and no family history have any criterion of hemolytic disease. Ten of these patients have normal younger sibs, and 5 are last-born. These cases showed very divergent clinical pictures.

In 1945, it was suggested by Yannet and Liebermann that A- and B-iso-immunization was a possible factor in the etiology of mental deficiency. As suggested by Yannet and others, this mechanism possibly might be more effective in the case of non-secretor children. We had no opportunity to study the secretor property. In spite of this, however, it was of interest to study the incompatibility situation of the 101 Rh-positive mental defectives and their mothers. The statistical calculations will be found in table 5. No significant differences were found between the figures observed and those calculated.

GENERAL DISCUSSION

The present investigation does not argue in favor of Rh-incompatibility being of practical importance in the etiology of undifferentiated mental deficiency. The possible existence of such a mechanism cannot of course be rejected simply on the basis of a statistical examination.

Yannet and Liebermann (1946) divided their patients into two groups: one comprising patients with well recognized diagnostic classifications, i.e., mongolian idiots, diplegia spastica infantum, cerebral infections and traumas, phenylpyruvic amentia, craniofacial anomalies, tuberous sclerosis, cerebral lipoidosis, and other conditions; the other group comprising patients with undifferentiated mental deficiency. The authors examined 119 patients with undifferentiated mental deficiency and 158 patients belonging to the first group, which served as control material. Mother-child Rh-incompatibility was found in 12 cases in the first group (7.6 ± 2.1 per cent) and in 19 cases in the second group (16.0 ± 3.3 per cent). A statistical calculation gives a P-value lying between 0.05 and 0.02. This difference can therefore hardly be considered statistically significant. Further, as pointed out by Cappell (1947), it cannot be correct to include three cases of erythroblastosis with nuclear jaundice in the undifferentiated group. If these three cases are excluded, there will be no difference at all between the undifferentiated group and the controls. After this correction, which seems justified, the result will agree with our own.

Snyder and co-workers (1946) reported the examination of 177 feeble-minded children and their 169 mothers. Of these children, 27 were Rh-positives from Rh-negative mothers. This was more than expected, and the difference is no doubt highly significant. However, 11 of these cases with Rh-incompatibility were subjected to a follow-up study (Scholl, *et al.*, 1947). One of these patients appeared to be a cretin. The mother of a second child was found on recheck to be Rh-positive. In no less than three instances was the feeble-minded child a

first-born. Only three of the 11 children had histories of neonatal jaundice. Anti-Rh antibodies were found only in one of the mothers. The authors conclude that only one of these cases could possibly have anything to do with the Rh-sensitization of the mother. The findings do not favor the theory of Yannet and Liebermann. This analysis of the incompatibility cases seems to rule out completely the conclusiveness of the previous statistical calculations. Unfortunately, the earlier communications of Snyder and his colleagues do not provide material for a discussion of the clinical diagnostic criteria. After the most recent paper (1947), it seems reasonable to assume that the differences between the statistical results in their material and ours may be fictitious.

CLINICAL AND PATHOLOGICAL REVIEW

Cerebral sequelae in children affected with severe jaundice were first described by Orth (1875). Since Schmorl's (1903) description, this clinical picture has been named kernicterus. This term, however, should be limited to the pathological changes, and we suggest *Rh-encephalopathy* to be introduced as the clinical designation. More recently, several investigations concerning the clinical features and pathology of this disease have been published. The reader is referred to surveys by Docter (1945) and Landé (1948).

Most authors agree that the histological changes are characterized by icteric discoloration chiefly of the caudate and lentiform nuclei; occasionally also the corpora mamillaria, the nucleus dentatus, and rarely the nuclei of the cranial nerves, the anterior and posterior horns of the spinal cord, and the cerebral and cerebellar cortex are discolored. Microscopically, demyelinization is seen, together with degeneration and pigmentation of the ganglion cells and proliferation of the glial tissue. Bilirubin deposits may also occur in the interstitial tissue.

It is obvious that the varying localization of the histological changes in nuclear jaundice may give rise to rather variegated syndromes, but the pictures of most cases coincide rather well. As mentioned above, it is hardly ever the first child that falls a victim of the disease. Signs of hemolytic disease of the newborn or prolonged icterus are characteristic features. The grade or duration of icterus plays no essential part in the severity of the consequent encephalopathy.

The cerebral signs are most often seen soon after birth, when they appear as convulsions, a tendency towards opisthotonos, a cry of "cerebral type", or tonic alterations. Not until later, during childhood, do the pronounced signs of cerebral damage become apparent. They consist of more or less universal rigidity—sometimes increased to muscular spasm—athetotic or choreatic movements of the arms and legs, grimaces, and general incoordination of movements. Muscular hypotonia may alternate with hypertonia, all of these signs

being due to extrapyramidal damage. They are diminished or absent during sleep. Hyperthermia may sometimes be observed.

Signs of pyramidal lesion, such as permanent spasticity and a positive Babinski phenomenon, may occur. In some cases ataxia and disturbances in the maintenance of equilibrium of a cerebellar type are noticed. A few patients squint, are amaurotic, or are hard of hearing, indicating an involvement of the cranial nerve nuclei.

The mental development reaches a varying degree, and, as pointed out by Parsons (1947), though the mental capacity of many of these patients is not below the average, they are often regarded as mentally deficient owing to the difficulty they have in expressing themselves. Profound mental deficiency has also been described.

Rh-encephalopathy must be differentiated especially from morbid states with different etiology in which there is a clinical picture indicating principally extrapyramidal lesions.

The syndrome known as encephalopathia infantilis comprises a fairly heterogeneous semeiotic notion: various congenital or early acquired morbid states with spasticity as a prominent feature in most cases and sometimes with co-existent intellectual inferiority. It is evident that cases of Rh-encephalopathy may be expected within this group of diseases.

Athétose double or Vogt's disease, with its striatal symptomatologic appearance, resembles Rh-encephalopathy. In the pure forms of Vogt's disease intelligence is normal, but cases with defective intellectual development have been described. In the latter variety, where cortical lesions must be assumed, the signs can be much the same as those of Rh-encephalopathy. Anamnestic data from the neonatal period are of paramount value in making the differential diagnosis.

Dystonias of various kinds, and above all, the torsion dystonias, as well as hepatolenticular degeneration, should be borne in mind when diagnosing Rh-encephalopathy.

Turning to the second question, namely the frequency of Rh-encephalopathy in the present total material of mainly *adult* mental defectives, the following cases may be presented.

CASE REPORTS

Cases 1, 2, and 3 concern patients who belong to our group *2c;* they have been excluded from the above calculations, since by signs and symptoms they may be referred to a special etiological group (nuclear jaundice) and are thus not "undifferentiated." Cases 4, 5, 6, and 7 are patients who did not fulfill the criteria for exclusion on etiological grounds but show signs and symptoms suggestive of Rh-encephalopathy. No. 5 was excluded as being a first-born child. Serological studies were not possible on the mothers of 4, 5, 6, and 7, so these cases are not considered in table 4. In other words, we present here all of the patients in the present study who have been diagnosed as Rh-encephalopathy irrespective of the above statistical calculations.

Case 1. A 29 year old man, B.H.N.A. (Vipeholm file number 42/43). The patient is the sixth of 7 children; the sibs are said to be normal. At birth he showed weak signs of life and was icteric, the jaundice lasting about one month. From early childhood he appeared to be mentally backward. He could walk at 4 to 5 years of age, and say a few words at 10 to 11 years. Dyskinesias, in the form of flinging movements of the arms and jerks of the neck, were observed by the patient's mother before he was taken care of in an institution for mental defectives at the age of nine. His hyperkinesias have increased in severity and there is a history of paroxysms of rage and aggressiveness. He is said to have had spells of depression with suicidal trends.

At Vipeholm Hospital he has been rather good-tempered and somewhat elated. His sense of hearing is not greatly impaired but his understanding of verbal suggestions is poor and he can utter only a few understandable words. His mental age is approximately 5 years. He shows no rigidity, lasting hypertonia, or marked muscular atrophy. Patellar and ankle jerks are vivid; plantar reflexes, extensor; but there is no typical Babinski toe sign. The gait is spastic-atactic. The patient is perpetually grimacing and contracting his Platysma; he contracts the muscles of his upper arms, bends the wrists vigorously, turns his head, and makes slight trunk motions—as if to restore slightly disturbed equilibrium. All of these hyperkinesias are absent in sleep.

Wassermann reaction, negative; E.S.R., 2 mm.; Formol-gel test, negative; Thymol turbidity test, positive (extinction at 0.55); Bilirubin, 0.2 mg. per cent, no direct reaction; Serum phosphatase, 4.5 Bodansky units. The patient is Rh-positive; his mother is Rh-negative, with anti-Rh antibodies demonstrable only in bovine albumin at a titer of 1:2. The sample was taken 20 years after the last pregnancy.

Case 2. A 32 year old male, A.G.S. (Vipeholm file number 58/44). The patient is the seventh of 8 children; the fourth child died of jaundice when but three days old, the sixth was still-born, and the youngest died of icterus five days after birth. One of the sibs still alive is said to be hard of hearing. The patient could walk at three years of age; he has never learned to talk, and was not clean until he was 7 years old. When he was a child his mother observed that he wriggled. He was sent to a school for deaf-mutes where he learned his three R's. Increasing irascibility and aggressiveness made it necessary to provide for him at an institution.

At Vipeholm Hospital he has been quiet and compliant, occasionally, but rarely, aggressive. He is hard of hearing, does not understand anything when spoken to, and is almost completely mute. Mental age is about 7 years as tested in a non-verbal way. The right pupil is slightly larger than the left; pupillary light reflexes are normal; the muscle reflexes of the extremities are vivid; plantar reflexes are flexor. Mayer's reflex is absent in the left hand. The left arm is hypertonic. No dyskinesias. The gait is ataxic without synkinesis of the left arm. Now and then a slight propulsion trend is evident.

Wassermann reaction, negative; E.S.R., 11 mm.; Formol-gel test, positive after 4 hours; Thymol turbidity test, positive (extinction at 0.50); Bilirubin, 0.2 mg. per cent, no direct reaction; Serum phosphatase, 2.2 Bodansky units. The patient is Rh-positive; his mother is Rh-negative and she had no anti-Rh antibodies.

Case 3. A 32 year old male, T.E.A. (Vipeholm file number 97/43). The patient is the second of four siblings, the last of whom was still-born. None of the sibs have been jaundiced.

On his fourth day of life the patient suffered from frequent convulsions, preceded by severe icterus. During his first year his parents observed that he was unlike other children; they could not remember when his dyskinesias first appeared. He could walk at five or six years, was clean at seven or eight years, but has never learned to talk. Since he was 9 years of age he has been kept at asylums, except for intermittant stays at home. He has been destructive and is liable to vehement attacks of wrath and aggressiveness.

At Vipeholm Hospital the patient has been calm most of the time. His hearing may be somewhat impaired, but he turns his head when spoken to in a rather loud conversational voice. He does not understand verbal commands except on a few—rather astonishing—occasions. He is not able to talk.

The patient has winged scapulae, hypertonicity in the trunk muscles and in the musculature of the lower extremity, but no lasting hypertonia in the upper extremities. The Babinski phenomenon is present bilaterally. The muscle reflexes of the arms are somewhat weaker on the right side; there is no certain asymmetry in the patellar and ankle jerks. The patient shows involuntary vertical movements of the tongue and the floor of the mouth, and lateral movements of the jaw. There are movements in the mimical muscles (quaint smiles) and in those of the neck (turning of the head). The right hand is bent at the wrist and the fingers are hyperextended and fanned; in the left hand there are flexions at the metacarpophalangeal joints. Rotating movements in the left shoulder joint are intermingled with the other movements, such as flexion at the right elbow-joint, hyperextension of the toes, and inversion of the feet. There are small balancing movements in the trunk muscles. His gait is ataxic. There is adiadokocinesis of the left arm. All of his hyperkinesias are absent in sleep.

The Wassermann reaction is negative; E.S.R., 6 mm.; Formol-gel test, positive within 3 hours; Thymol turbidity test, positive (extinction 0.56); Bilirubin, 0.2 mg. per cent, no direct reaction; Serum phosphatase, 5.9 Bodansky units. The patient is Rh-positive; his mother is Rh-negative, lacking anti-Rh antibodies. The sample was taken 21 years after the last pregnancy.

Case 4. A 39 year old male (Vipeholm file number 11/37). The patient was icteric a little more than a month from the fourth day of life. He has torsion dystonia of the same character as in cases 1 and 3. He is hard of hearing, but not deaf. He does not understand verbal commands, has impulsive attacks of rage. Thymol turbidity test: negative. The patient is Rh-negative; his mother is dead.

Case 5. A 41 year old male (Vipeholm file number 24/45). The patient was born as the first of 4 children. His involuntary movements began when he was five years old without preceding signs of illness. He has a clinical picture strongly reminiscent of cases 1, 3 and 4. The patient is Rh-positive; his parents are dead.

Case 6. A 32 year old female (Nyhem file number 570). She is the eldest of 7 siblings. There was no icterus at birth. She can see and hear well, but cannot walk nor feed herself. She utters only unintelligible words. She grimaces and has everlasting athetotic movements in her arms and hands, as well as synkinesias in her trunk and neck. Hypertonicity, with rigidity in the upper extremities, is present, and there is adductorial spasm in the legs. She exhibits no Babinski phenomenon or other reflex anomaly. She is Rh-positive; it has not been possible to obtain a blood sample from her mother.

Case 7. A 40 year old female (Nyhem file number 497). She is the seventh of 11 siblings, five of which are dead of various diseases during infancy and childhood. One younger sib is feeble-minded; the rest of the living siblings are well. There was no icterus. The patient was found to be mentally retarded at about three years of age. She is hard of hearing, has a disturbed equilibrium and permanent athetotic movements in both her arms, hands, and fingers. Muscular rigidity is present, and she is frequently grimacing. Her speech is inarticulate and spluttering. The reflexes are normal. She is Rh-positive; her mother is dead.

DISCUSSION OF RH-ENCEPHALOPATHY

To establish the diagnosis of Rh-encephalopathy one should be able to (1) verify serologically an Rh-incompatibility between the patient and his mother, (2) ensure a history of hemolytic disease of the new-born, and (3) demon-

strate neurological changes of a predominantly extrapyramidal character, with or without mental deficiency. Our cases 1, 2 and 3 fulfill these conditions. In case 4, the presence of Rh-encephalopathy seems rather probable, although serological support of the diagnosis is lacking, since the patient's mother is dead. Cases 5 and 6 are first children—which disagrees with the conception of Rh-incompatibility as a cause of their extrapyramidal signs. They may be referred to the group of cryptogenic torsion dystonias, or possibly *athétose double*. In case 7 the diagnosis is also debatable.

The first three cases, in which there is a definite diagnosis of Rh-encephalopathy, show a positive thymol turbidity test, indicating a latent impairment of the liver parenchyma, persisting for about 30 years. These findings must be seen in the light of the observations that a positive thymol turbidity test occurs within other etiologic groups in our material.

Another common trait in these cases of Rh-encephalopathy is the disturbance in perception of the spoken language, which is not wholly explained by the patient's hardness of hearing and does not correspond to the degree of mental depravation. This phenomenon is likewise found in association with other injuries of the brain. In addition to the dysarthria and other motor disturbances, the sensory aphasia makes difficult an accurate evaluation of the intellectual capacity. In our cases, however, an undoubted imbecility is manifest.

In estimating the occurrence of Rh-encephalopathy in this material, we have 3 cases with a definite diagnosis, one case with a fairly well-founded diagnosis (case 4), and one with a doubtful diagnosis (case 7). We thus arrive at the percentages of 0.3, 0.4, or 0.5 among the total of 977 mental defectives. It should be noted, however, that this is mainly an adult material and it seems very probable that an examination of a younger material will give a higher figure.

SUMMARY

1. With a view of detecting signs and symptoms referable to mother-child incompatibility of blood groups, 977 predominantly low-grade mental defectives were studied clinically and serologically.

2. The distribution of the different blood groups (A-B-O and Rh systems in the total series coincides within statistical limits with that found in unselected samples of the Swedish population. The blood group distribution in a group of mental defectives classified as "undifferentiated feeble-mindedness of unknown etiology" was also normal.

3. After a suitable selection (Rh-positive mental defectives, not first born, of unknown etiology and undifferentiated clinical picture) the mothers of 101 such patients were examined. Fifteen mothers were Rh-negative. This figure coincides statistically with the expected frequency calculated for the Swedish population.

4. For the fifteen patients with mother-child incompatibility neither anamnesis nor clinical data produced evidence of *Rh-encephalopathy*. The latter term is introduced to designate the clinical picture of patients with Rh injury of the central nervous system; the term kernicterus or nuclear jaundice should be limited to the pathological anatomical description.

5. In the total material of 977 mainly adult mental defectives, three cases were found which permitted a rather clear-cut diagnosis of Rh-encephalopathy. This gives a frequency of 0.3 per cent.

6. The main conclusion of this study is that hemolytic disease of the newborn or simply mother-child Rh-incompatibility is not an important etiological factor of undifferentiated mental deficiency. In our material this mechanism seems to be of little or no practical significance.

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Chromatid Bridges and Fragments in Human Spermatocytes

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KOLLER, in 1937, reported a study of the chromosomes in human testis. One of the three individuals from whom his material was taken was, apparently, heterozygous for an inversion, for a number of first spermatocyte anaphases and telophases were found which contained chromatid bridges and fragments. This condition, in plants and lower animals, is known to be one of the consequences of a crossover in an inversion loop which does not include the centromere. Single crossovers and three- and four-strand double crossovers in such a loop give rise to dicentric chromatids and acentric chromatid fragments. The two ends of a dicentric chromatid move toward opposite ends of the spindle and the chromatid is stretched and breaks as the cell divides. An acentric fragment, not being attached to a spindle fiber, fails to move towards either pole and is eventually lost in the cytoplasm.

Recently one of us (E.H.S.), while examining a slide of human testis which had been prepared by the other (H.W.B.), found an anaphase of a primary spermatocyte with a chromatid bridge (figs. 1 and 2). The detailed history of this particular slide—an exceptionally fine one—has not been kept, but it is one of a large number made about fifteen years ago. The material from which it was prepared was obtained, at operation, from a group of young males aged, respectively, 15, 16, 18, 19, 25 and 26 years. Specimens from different individuals were not kept separate. Each testis was cut into small fragments immediately upon removal from the body. These were fixed in Allen's B15, sectioned at 7.5 μ and stained in Heidenhain's iron-alum hematoxylin. Other material obtained at the same time, some of which was fixed and stained in different ways, has been used in several studies reported earlier (Gatenby & Beams, 1935; King & Beams, 1936).

The relationship of the slide on which this unusual spermatocyte was found to others in the same series has been lost and, as a result, the observations reported here are limited to this one slide. Fortunately, however, it has on it twenty-five sections, each of which is approximately 5 mm. long and 3 mm. wide, and so furnishes a considerable amount of material for study.

After the cell shown in figures 1 and 2 was found, a search for all of the spermatocyte anaphases and early telophases on the slide was undertaken.

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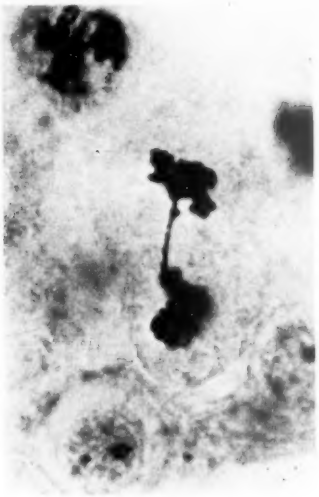

FIG. 1. Photomicrograph of human primary spermatocyte anaphase with chromatid bridge; no fragments. × 1800.

FIG. 1

Only ten were found which were in a satisfactory stage and position for study.[1] As Koller (1937) remarks, anaphases are uncommon, which indicates that this stage must be passed through very rapidly. Of the ten anaphases and early telophases found, three, because of their smaller size, are probably secondary spermatocytes. This leaves seven which can be identified with some certainty as primary spermatocytes.

Besides the primary spermatocyte shown in figures 1 and 2, one other with a bridge was found. This spermatocyte (fig. 3) is in telophase, and cell division has begun but the bridge has, apparently, prevented the two groups of chromatids from moving farther apart. The lowermost group of chromatids is smaller than the other. A darkly-stained body in the upper part of the dividing cell is probably the X chromosome. Five primary spermatocyte anaphases with no bridges or fragments are shown in figures 4 to 8. In four of these chromatin strands extend part way across the gap between the two masses of chromatids. The cells shown in figures 9, 10 and 11 are apparently secondary spermatocyte anaphases. In two of them small, dark-stained bodies are present between the two groups of chromatids. These may or may not be acentric fragments.

[1] In addition to the anaphases described here several others were found. All, however, are in early or mid anaphase and the two groups of chromatids have not yet reached the poles. In each of these, one or more of the daughter chromosomes is still in contact with the other in the region of the equatorial plate. Evans and Swezy (1929, fig. B9 and fig. 51, pl. VI) illustrate stages of this type. It is impossible to tell whether bridges are or are not present in such cells. They have been omitted from consideration in this study.

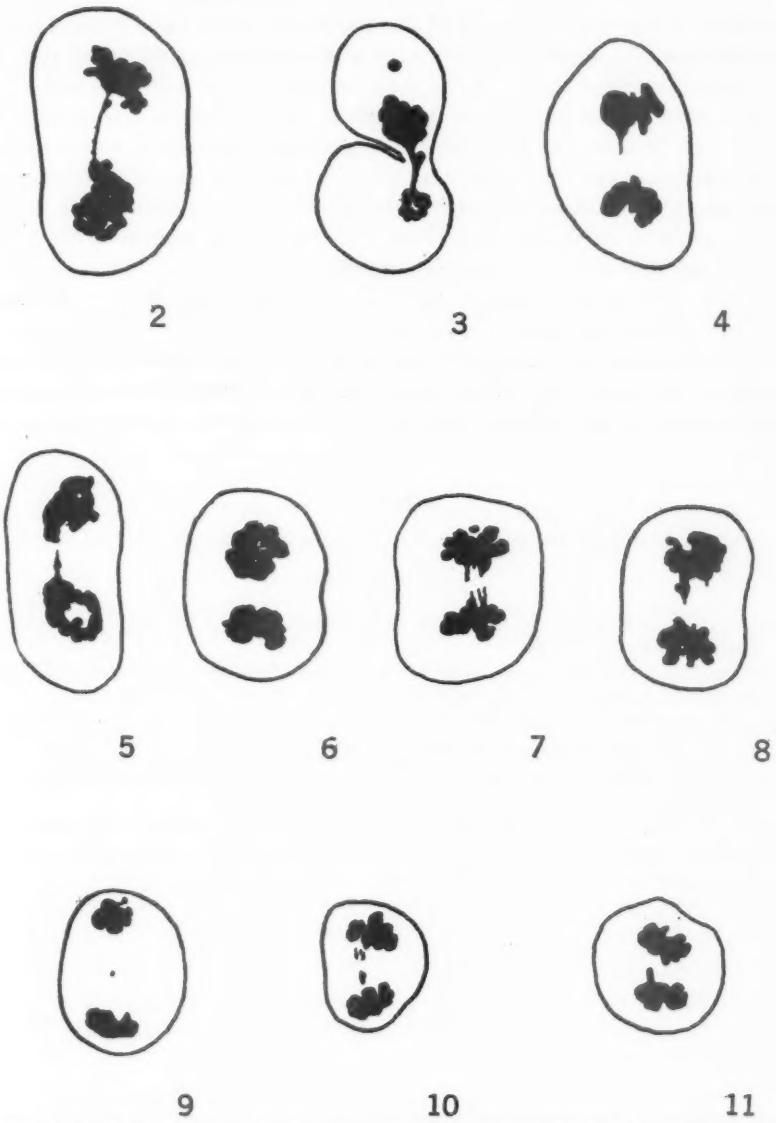

FIG. 2. Anaphase of human primary spermatocyte with chromatid bridge. Photomicrograph of this cell is shown in fig. 1. × 1800.

FIG. 3. Telophase of primary spermatocyte with chromatid bridge and X-chromosome (?) in upper cell. × 1800.

FIGS. 4–8. Anaphases of primary spermatocytes; no bridges or fragments. × 1800.

FIGS. 9, 10. Secondary spermatocyte anaphases with fragments (?). × 1800.

FIG. 11. Secondary spermatocyte anaphase; no fragments. × 1800.

Schultz (1946) and Schultz and St. Lawrence (1949) have studied smear preparations of the cells from the testes of 40 individuals and report that for one particular chromosome, which is associated with the nucleolus and has a definite chromomere pattern recognizable at pachytene, no inversions have been found. Schultz and St. Lawrence suggest that the structures described as bridges and fragments by Koller may actually represent "adhesions of chromosome ends" and "laggard smaller autosomes." In the present state of our knowledge it is obviously impossible to decide which interpretation is the correct one. However, it is probably significant that Koller found all of his abnormal cells in the testicular material from one of the three individuals which he studied and none in that from the other two. The same appears to be true in the present study. All of the unusual ~~anaphases and telophases~~ spermatocytes were found on one slide. Other slides, with material presumably from other individuals, have, so far, failed to show any abnormalities of the type described here.

SUMMARY

A new instance of an apparent chromosome inversion in man is reported.

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Microcytemia, Constitutional Microcytic Anemia, and Cooley's Anemia
(Mediterranean Anemia or Thalassemia)

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MICROCYTEMIA AND CONSTITUTIONAL MICROCYTIC ANEMIA

IN the course of some investigations on the behavior of red cell fragility in patients affected with cancer (Silvestroni & Bianco,1943) we observed the presence of a decreased red cell fragility in some otherwise normal individuals taken as controls. We therefore extended our research (1943–44, 1944) to a larger number of normal subjects (400) and found that seven among them showed a decreased corpuscular fragility. A more complete hematological investigation rendered evident that these persons had, besides a decreased corpuscular fragility, an unusually high red cell count, hypochromia, and microcytosis. This complex of hematological traits or hematological anomaly—*microcytemia* as we called the manifestation (1945–46*a*, 1946*a*, *b*)—was shown to be transmissible as a Mendelian dominant in both sexes.

At the same time (1943–44) we observed the similarity of these hematological traits to those shown by patients affected with so-called hemolytic icterus combined with decreased corpuscular fragility, called by us now *constitutional microcytic anemia* (Silvestroni, 1944; Silvestroni & Bianco, 1946*c*). This disease was described for the first time in Italy by Rietti in 1925, and afterwards illustrated under other names by a number of Italian and American authors (Greppi, 1928,1931; Micheli, 1929; Testolin & Angelini, 1933; Usseglio, *et al.*, 1934*a*, *b*; Introzzi, 1935; Micheli, *et al.*, 1935; Crosetti & Bajardi, 1935; Bettoni, 1935; Testolin, 1936; Momigliano Levi, 1937; Sansone, 1938; Specie, 1941; Pontoni, 1942; Wintrobe, *et al.*, 1940; Dameshek, 1940; Smith, 1941; Strauss, *et al.*, 1941). It is a familial disease on a constitutional basis, characterized by a slow and generally benign evolution, a mild subicterus (less frequently by an icterus), splenomegaly of various degrees, anemia resistant to iron therapy, weakness, and a moderate hyperhemolysis.

Already during the first investigations we adumbrated the hypothesis that the form of hematological anomaly (microcytemia) detected by us in normal individuals could represent the necessary constitutional background on which microcytic anemia could develop, being caused by additional unknown factors.

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In fact, one of us (Silvestroni, 1944) could demonstrate, after studying all the cases recorded in Italy, that it is possible to pass by imperceptible degrees from healthy individuals, through carriers of the hematological anomaly, to individuals affected with the full-blown disease. Because of the fact that microcytic anemia takes its origin from the hematological anomaly, and because of various other factors, this morbid form was distinguished by Silvestroni from the constitutional hemolytic icterus (in opposition to the opinion of several other investigators who consider it to be a variety of the latter disease). He considered it as a clearly defined morbid entity, which he called constitutional microcytic anemia, by reason of its most outstanding clinical and hematological features.

In subsequent investigations (1944–45*a*, 1945) of the carrier state, we detected 88 carriers of the anomaly among 1500 individuals examined, and we could observe the whole range of clinical pictures, from the carriers of the anomaly in perfect health, who constituted the greatest part of the subjects, to the patients with a more or less manifest form of constitutional microcytic anemia. We demonstrated the inconstancy of the signs of hyperhemolysis in normal individuals and, on the contrary, the frequency of them in individuals showing other signs of illness. In addition to the above mentioned hematological traits, we noted the frequent morphological alterations of the red cells, from an almost normal appearance to the more evident picture of aniso-poikilo-ellipsocytosis and hypochromia, with target cells and polychromatophil cells or stippled cells.

From observations (1946*c*) made on 9 patients affected with constitutional microcytic anemia, we could trace the clinical and hematological picture of the disease, especially in its milder forms, as yet little known, and we remarked in each case that it is a familial disorder and that its onset occurs on a constitutional background of microcytemia.

In the same year (1946*a*, *b*) we made an analytic study of each hematological feature of microcytemia, as observed in 224 carriers of the anomaly. We analyzed particularly the problem of hyperhemolysis, and concluded that this characteristic, manifesting itself in a very mild form in only a third of the healthy carriers of microcytemia, does not represent a primitive constitutional character, but it is only one of the most frequent and early signs which accompany the onset of the disease (i.e., constitutional microcytic anemia).

As to the origin of microcytemia we suggested (1945–46*a*, 1946*a*, 1946*b*) that the disorder is caused by a change of a gene connected with the erythropoietic system, such change or mutation occurring in some human stock (1948*a*) and originating a new type of red cell differing from the normal erythrocyte by being smaller, poorer in hemoglobin, and more resistant to hypotonic solutions.

One of us, collaborating with Gentili (Silvestroni & Gentili, 1945–46, 1946) could demonstrate the presence of special anthropological characters in the carriers of microcytemia. Over half of the 107 individuals examined were found to possess a concave nose with sunken root and thickened flat tip, and there was evidence of a peculiar conformation of the cheek bones, with anterior and lateral flattening of the zygomatic area. Collectively these traits were called *facies microcytemica* by Silvestroni & Gentili, who adumbrated two different hypotheses to account for them: they may be the expression of a racial character pertaining to a particular human stock, or a constitutional one going along with the presence of microcytemia. Interestingly, the deviations found in *facies microcytemica* are reminiscent of the more pronounced changes (*facies mongoloides*) which have frequently been noted in cases of Cooley's anemia.

Very recently (1949*a*) we carried out a detailed comparison of the hematological features of 202 microcytemic individuals and of 100 normal Italian subjects. The hematological picture of microcytemia can be differentiated from the normal blood picture by a number of constant and closely related characteristics: (1) hypochromia, with a color index always less than 0.80, (2) an almost invariably elevated red cell count (from 5.5 to 6.5 millions in males, from 5.0 to 6.0 millions in females); (3) a decreased red cell fragility (the value of maximal resistance, with Viola's method, ranging from 0.18 to 0.28 and the value of minimal resistance from 0.36 to 0.44); (4) a true microcytosis, shown by a volume index ranging mostly from 0.70 to 0.85 (while in normal individuals it ranges from 0.93 to 1.10); and (5) the morphological erythrocytic alterations above mentioned, which are more or less evident. These new investigations confirm that microcytemia is a deep-seated and complex alteration which affects in different ways the whole red cell, and makes it distinguishable, as a rule, from the normal red cell. Frequently the anomaly is apparent at first sight in the counting chamber. However, we must say that in our investigations we have encountered on rare occasions subjects who showed a form of microcytemia with such slight deviations that it was doubtful if they were microcytemic or normal subjects.

POPULATION STUDIES

Since 1944 we were interested in the geographical distribution of microcytemia in Italy (Silvestroni & Bianco, 1944–45*a*, 1945, 1946–47*a*, 1947*a*, *b*, 1948*b*, *c*, 1949*b*, *e*; Bianco,1948). In fig. 1 we show, alongside the map of Italy, the numbers of examined individuals in the different areas, the numbers of detected microcytemic subjects, and the percentage frequencies of microcytemia. Collectively we have examined more than 30,000 individuals.

It should be explained that in our general population studies, executed on rather large groups of individuals, it was not possible to make complete hema-

tological examinations concerning the various features of microcytemia; instead we resorted to a more rapid, simplified technic. We observed that in the 0.4 solution of Simmel's method (Simmel, 1923), the red cells of normal subjects undergo a practically complete hemolysis, and that the fluid contained in the pipette becomes clear in a few minutes; but the red cells of microcytemic subjects instead, as they are more resistant to hypotonic solutions, undergo only partial the hemolysis, so that the fluid contained in the pipette remains always more or less intensely opaque. In our examinations we always started with the erythrocyte fragility test in order to detect the microcytemic individuals. Thus we observed that the increased red cells resistance in otherwise normal individuals revealed always the presence of microcytemia.

In the above mentioned population surveys we tested, in all the examined individuals, the red cell fragility with the 0.4 solution of Simmel's method. At the same time, we also took a blood smear in order to observe, in doubtful cases of microcytemia, the morphological changes of the red cells. In this way we examined a great number of individuals in a rather short time. Perhaps a few cases of microcytemic individuals having a very slightly decreased red cell fragility were not detected with this method. But from the whole of our studies it appears that such cases are very rare and therefore the percentages of microcytemia found by us in various regions of Italy are reliable.

From the data shown in fig. 1, it is seen that among the sampled areas, the provinces of Ferrara and Rovigo (viz. all the lands around the Po delta) show the highest frequency of microcytemic cases (10.22% and 9.73% respectively). In this area, especially in the province of Ferrara, where we made more numerous tests, there are some villages in which the frequency of microcytemia is even higher: 12.4% at Copparo, 15–16% in some still smaller villages (Silvestroni & Bianco, 1948*b*). But if we pass from the province of Ferrara to the nearby province of Bologna, the frequency of microcytemia falls to a mere 0.8%. Among the other continental regions of Italy, Puglie and Calabria show a rather high frequency of microcytemia (5.6% in the province of Lecce, 3.5% in the province of Reggio Calabria) while other regions of central and northern Italy, excepting the above mentioned regions around the Po delta, show very low percentage values.

Already in our first studies made in Rome (1945) on 1500 individuals, we observed that the detected carriers of microcytemia came principally from Sicily and Sardinia. In the summer of 1948 we went to Sicily and investigated the frequency of microcytemia in the more important towns and in various villages on the coasts and in the interior of the isle (1949*c*). In figure 1 the frequencies of microcytemia in the various Sicilian provinces are listed. The anomaly was present and rather frequent in the different parts of the island, but was not evenly distributed: there are villages along the Meridional and Oriental coasts of Sicily where microcytemia is very frequent (10.81% at

Ribera, 8.81% at Gela, 8.27% at Lentini), while in other villages or towns also not far removed; the abnormality is much less frequent (3.64% in the town of Catania, 2.86% in the town of Messina, 2.79% in the town of Caltanissetta). Altogether, on 6739 examined individuals, the frequency of micrycytemia in Sicily was found to be 4.45%.

From all our investigations made in Italy it results that microcytemia is particularly frequent only in the Meridional and Insular regions and in the provinces of Ferrara and Rovigo. It is interesting that in the explored towns of central and northern Italy, where the frequency values of microcytemia are very low, a good portion of the detected microcytemic individuals were found to originate from the regions in which microcytemia is more frequent. This

Locality	Number Tested	Microcytemic Number	Per cent
Torino	1,174	11	0.94
Milano	1,072	15	1.40
Genova	1,156	18	1.56
Padova	1,082	22	2.03
Rovigo	955	93	9.74
Ferrara	6,602	675	10.22
Ravenna	216	8	3.70
Bologna	229	2	0.87
Firenze	417	2	0.48
Ancona	787	13	1.65
Roma	7,595	125	1.65
Napoli	1,668	34	2.04
Lecce	620	33	5.32
Reggio C.	371	13	3.50
Palermo	1,428	61	4.27
Agrigento	1,032	65	6.30
Caltanissetta	1,075	42	3.91
Siracusa	992	50	5.04
Catania	1,584	65	4.10
Messina	628	18	2.87

FIG. 1. Distribution of microcytemia in Italy and Sicily.

shows that microcytemia in Italy is slowly spreading from some limited foci to originally free regions (Silvestroni & Bianco, 1949*b*).

Recently (1948*a*) we described the first cases of microcytemia and constitutional microcytic anemia in Egyptian subjects.

GENETIC STUDIES

Starting from the observation that many analogies exist (hematological, genetic, racial) between patients affected with constitutional microcytic anemia and those affected with Cooley's anemia, and having already demonstrated that constitutional microcytic anemia arises on a constitutional background of microcytemia, we undertook to investigate (1945–46*b*) whether Cooley's anemia might originate from the same anomaly.

We carried out our first study (1945–46*b*, 1946*d*, 1946*e*) of Cooley's anemia in Rome, during the summer of 1945. For this purpose we examined the families of 38 children most of whom had been hospitalized, in the ten years previous to our investigation, with a diagnosis of Cooley's anemia, or of anemia of Jaksch-Hayem-Luzet, or of acute erythremic myelosis. In 22 families we found microcytemia present in both parents, but in 7 families it was found in only one parent, and in the remaining 9 families microcytemia was absent in both parents. Most of the children affected with Cooley's anemia whose parents showed microcytemia had already died in consequence of the disease, and the few who were still living were seriously ill. On the other hand, the children born of parents who did not exhibit microcytemia were almost all still living and fully recovered. These investigations demonstrated the existence of an etiopathogenetic correlation between microcytemia and Cooley's anemia. In the cases occurring in families where only one parent showed microcytemia and which were nevertheless diagnosed as cases of Cooley's anemia, we supposed that the parent who failed to exhibit microcytemia was probably the carrier of another factor which, though harmless in itself, had a noxious effect if associated with microcytemia. This theory is supported by our observations of morbid pictures which were fully similar to Cooley's anemia, occurring on a genetic background of two different hematological anomalies: microcytemia and sicklemia (Silvestroni & Bianco, 1944–45*b*, 1945–46*c*, 1946*f*, 1946*g*).

In further investigations (1946–47*a*, 1947*a*, 1948*c*) made at Ferrara in the summer of 1946, the families of 40 patients affected with Cooley's anemia, were studied, and a total of 154 relatives were examined. In 38 families the evidence of microcytemia was noted in both parents, as well as in numerous siblings of the patients, but in 2 families only one of the parents showed the anomaly.

In a third group of investigations (1946–47*b*, 1947*c*, 1948*f*) we examined from a clinical, hematological and genetic point of view 23 cases of Cooley's anemia, 17 cases of constitutional microcytic anemia, and 2 cases of a morbid syndrome which was clinically similar to Cooley's anemia but which had a different genesis. In each case of Cooley's anemia we found evidence of microcytemia in both parents, while in the cases of constitutional microcytic anemia the microcytemia was observed in only one of the patient's parents or in only a part of his children. In the 2 cases of the syndrome similar to Cooley's anemia the microcytemia was present in only one parent, and in one of these cases the parent lacking microcytemia was a carrier of constitutional ovalocytosis (Silvestroni & Bianco, 1944–45*c*, 1946*h*, 1948*d*).

These three groups of investigations demonstrate the strict connection between Cooley's anemia and microcytemia and illustrate the fact that in most cases this disease occurs in families in which both parents are carriers of microcytemia. This suggests that Cooley's anemia may be due to the homozygous

condition of the gene producing microcytemia. In fact, those cases occurring in families in which only one parent was found to possess microcytemia, and classified as Cooley's anemia, are supposed by us to be either (1) forms of a disorder similar to Cooley's anemia ("Cooley-similar syndromes", cf. Silvestroni, 1947; Silvestroni & Bianco, 1948*f*) due to a genetic association of microcytemia with another constitutional factor (e.g., *sicklemia*, cf. Silvestroni & Bianco, 1944–45*b*, 1945–46*c*, 1946*f*, 1948*e*, 1949*d;* or *ovalocytosis*, cf. Silvestroni & Bianco, 1948*f;* or another yet unidentified factor), or (2) true cases of Cooley's anemia in which the microcytemia of one parent was not recognized because of its very mild form—and we noticed it recently in some families in which the microcytemia could be detected in two or more children although it was very difficult to recognize in the parent who transmitted it—or finally, (3) cases of Cooley's anemia in which the paternity was different from the one stated. Also, by way of explaining the occurrence of Cooley's anemia in families in which only one parent showed microcytemia, we must point out that some of the patients in our first study had died prior to our examination of their parents, and the diagnosis of Cooley's anemia had been made at a time when the disease was still little known, so the possibility of diagnostic errors cannot be excluded.

As to constitutional microcytic anemia, our studies already cited (Silvestroni & Bianco, 1946–47*b*, 1947*c*, 1948*f;* Silvestroni, 1947, 1948) have shown that it is based upon the heterozygous state of the genetic factor for microcytemia, and this fact forms a differential criterion of great value in distinguishing the disorder from Cooley's anemia.

Even before our own investigations were reported, some isolated reports (Micheli, *et al.*, 1935; Wintrobe, *et al.*, 1940; Dameshek, 1940) pointed out the existence of a relationship between Cooley's anemia and constitutional microcytic anemia, the latter being considered as an attenuated form of Cooley's anemia. On the other hand, there were systematic researches (Angelini, 1937; Caminopetros, 1937; Gatto, 1942) which demonstrated the presence of some abnormal hematological traits (especially decreased corpuscular fragility) in the parents of patients affected with Cooley's anemia.

After the war, when the cultural relations among the different countries were again established, we became acquainted with a number of studies made since 1941 by investigators in the United States (McIntosh and Wood, 1942; Dameshek, 1943; Smith, 1943; Valentine and Neel, 1944; Neel and Valentine, 1945, 1947). By the examination of a certain number of families originating in Greece and Italy these workers observed a mild form of anemia, characterized by increased red cell count, hypocromia, microcytosis, decreased corpuscular fragility and various morphologic alterations of the red cells. It was transmissible as a Mendelian dominant. This mild form of anemia, regarded by the same authors as an attenuated or benign form of Cooley's anemia, was found

in both parents of patients affected with Cooley's anemia. Therefore it was concluded (Dameshek, 1943; Valentine and Neel, 1944) that, while the mild affection or *thalassemia minor* is the expression of a gene in heterozygous state, the serious affection or *thalassemia major* or Cooley's anemia is the expression of the homozygous condition of the same gene. It is interesting that Neel and Valentine (1945), working with a population of Italian-American families derived principally from Sicily and southern Italy, arrived at an estimated incidence of thalassemia minor (microcytemia) of 4.1%, a value which agrees remarkably well with the average incidence found by us in Sicily, viz., 4.45% (figure 1).

All these results clearly agree with the results of our investigations. But instead of dividing the carriers of microcytemia in two groups (patients with thalassemia major and patients affected with thalassemia minor) we divide them in three groups: healthy carriers of microcytemia, patients with constitutional microcytic anemia, and patients with Cooley's anemia. Moreover, we remarked (1948*f*) that, whereas between healthy carriers of microcytemia and patients affected with constitutional microcytic anemia there is a whole range of intermediate morbid pictures, between patients with Cooley's anemia and those with constitutional microcytic anemia there is, on the contrary, a constant and remarkable difference in the clinical picture. Evidently this difference is attributable to the different genetic substratum of the two blood disorders (Cooley's anemia is homozygous, whereas constitutional microcytic anemia is heterozygous).

In our first investigation concerning healthy carriers of microcytemia and patients affected with Cooley's anemia (1946*a*, *d*), while studying the hereditary transmission of the anomaly, we remarked that the proportions of children who were heterozygous carriers of microcytemia, of children lacking microcytemia, and of homozygous children, did not correspond to the proportions required by the Mendelian law of dominance for the corresponding types of marriages. In fact, in the families having one microcytemic and one normal parent, $\frac{2}{3}$ of the children were found to be carriers of the anomaly, and $\frac{1}{3}$ were normal; in the families wherein both parents exhibited microcytemia, $\frac{1}{4}$ of the children were affected with Cooley's anemia, $\frac{1}{2}$ were heterozygous carriers of the anomaly, and $\frac{1}{4}$ were normal. Surprised by this particular result, we extended our investigations (1947*d*) to a greater number of cases, observed mostly at Ferrara in the summers of 1946 and 1947. In all, we examined 346 families of microcytemic individuals, 44 of them containing children affected with Cooley's anemia. In 67 families in which one parent was the proband and the other was normal, we found 85 microcytemic and 80 normal children among the 165 children examined. In another group of 188 families of the same type as the precedent ones, but in which the proband was a child, among 652 examined children 412 were found to be carriers of microcytemia and 240

were normal. However, introducing the correction formula adopted by Neel and Valentine: $r = .500\ N \pm .500\sqrt{N}$, where r is the expected number of microcytemic sibs of the proband carriers of microcytemia, and N is the total number of sibs of the probands, the expected number of microcytemic sibs becomes 232 ± 10.7, thus approaching the observed number, 224. In the 44 families in which the proband is a child with Cooley's anemia and both parents are carriers of microcytemia, of the 104 children examined, excluding the probands themselves and all sibs having Cooley's anemia, 63 sibs were carriers of microcytemia and 41 were normal. Again the figures are very near the theoretical ones reckoned with the formula adopted by Neel and Valentine: $r = .667\ N \pm .471\sqrt{N} = 69.36$ carriers, and $N - r = 34.64$ normal sibs. In the same families, the number of affected children (63) approaches remarkably well the number expected on the basis of Weinberg's formula of correction, which gives 74.75.

Besides these more numerous groups of families, other minor groups (we do not illustrate them for brevity's sake) confirm the hereditary behavior of microcytemia as a simple Mendelian dominant. It is thus demonstrated that, consistent with Mendelian expectations, in families where only one parent is a heterozygous carrier of microcytemia, the offspring are normal in half of the cases and in the other half they are carriers of microcytemia; in families in which both parents are heterozygous carriers of microcytemia, the children affected with Cooley's anemia amount to $\frac{1}{4}$ of all the offspring, namely to the incidence of homozygous children, while normal children correspond to another fourth and the microcytemic children to half of the offspring. Thus the discrepancy already observed, i.e. an excess of microcytemic children and of children affected with Cooley's anemia, is completely explained by the selective sampling.

In our second series of examinations made at Ferrara, during the summer of 1947, we also studied the distribution of the ABO blood groups in the microcytemic individuals (1947*b*). We examined for this purpose 1,580 individuals of both sexes and of varying ages; of these 715 were carriers of microcytemia, 842 were normal, and 23 were affected with Cooley's anemia. We found: (1) the carriers of microcytemia belong indifferently to the various blood groups; (2) microcytemia and blood group are independently transmitted from parents to their children; (3) in microcytemic individuals there is a light prevalence of group O (44.51%) over group A (42.13%), while in normal individuals of the same region the group A (45.18%) prevails over group O (40.03%); (4) in the patients affected with Cooley's anemia the prevalency of group O (52.17%) over group A (30.43%) is still more marked. But the biochemical race index does not differ for carriers of microcytemia from that of normal individuals, while in the patients with Cooley's anemia it is a little lower.

SUMMARY

Our investigations have demonstrated a particular constitutional hematological anomaly existing in the Italian population, *microcytemia*, which is hereditarily transmissible as a Mendelian dominant, and is independent of blood group and sex. It is characterized by an increased cell count, hypochromia, microcytosis, decreased red cell fragility, and morphologic alterations of the erythrocytes, the latter consisting in an aniso-poikilo-ellipsocytosis of varying degree, and in the presence of "target" cells, or polychromatophil cells or stippled cells. This anomaly is very frequent among the inhabitants of some provinces and regions of Italy (provinces of Ferrara and Rovigo, Sicily, Sardinia, Puglie) and it is less frequent in other regions (Lazio and the remaining regions and provinces of central and northern Italy). Microcytemia at the heterozygous state does not usually prevent good health, but in some cases it produces a constitutional microcytic anemia; at the homozygous state, instead, it produces Cooley's anemia.

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Paget's Disease (Osteitis deformans) and Heredity

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PAGET'S DISEASE or osteitis deformans was first described by Sir James Paget in 1876. The disease is characterized by a softening followed by an overgrowth of bone. During the period of softening the bones may undergo deformation. Several bones may be affected (polyostosis) or the disease, more rarely, may be confined to a single bone (monostosis).

The most conspicuous pathologic changes are seen in the pelvis, skull, the bones of the legs, and in the vertebral column.

Microscopically, bone is at first seen to be replaced by connective tissue, followed by a substitution of finely porous cancellous bone which gradually hardens. The process of apposition overtakes that of absorption, and the bone gradually thickens into a semi-solid network of soft trabeculae. The mosaic-like irregular segments of lamellar bone with their scalloped cement lines are uniquely characteristic of this disease.

The disease occurs in both sexes, and so far as is known occurs in all ethnic groups.

Paget's disease is rarely the cause of death.

In describing its clinical features Boyd (1947) states that the disease usually begins after the fortieth year. He suggests that it may be familial, and adds that he knows of two families in each of which three cases occurred.

In point of fact there are records of more than 30 families in each of which one or more other relatives exhibited the condition. A study of the cases reported in the literature suggests that the inheritance of Paget's disease is far from simple. The disorder is transmissible through each sex, and it appears likely that the gene involved is carried on an X-chromosome. It will, however, be necessary to collect many more family histories of Paget's disease than we at present have before its mode of inheritance can be definitely determined. Toward this end I should like to add one more family history of Paget's disease here.

During a routine medical examination made some 8 years ago the propositus, a white American Jewish male, was apprized of the fact that the x-ray films of his pelvis and skull bones showed the characteristic evidences of Paget's disease, namely, diffuse areas of finely mottled osteoporosis.

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I obtained the history from him which is pedigreed in fig. 1. On the face of this history it would seem that the propositus' mother and his maternal aunt acquired the gene from one or other of their parents, the propositus having in-

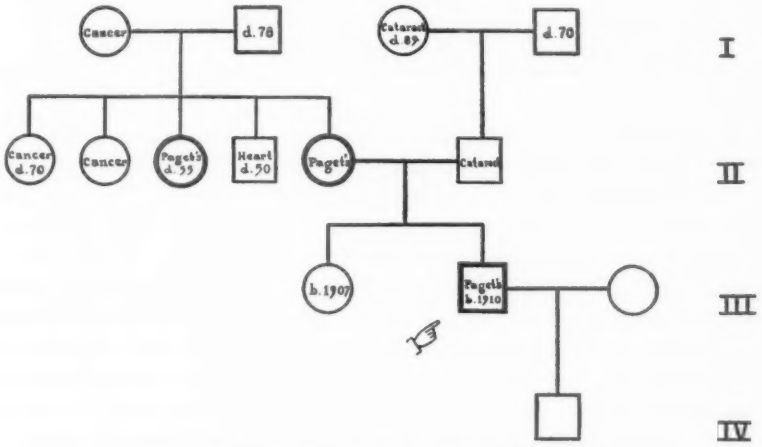

FIG. 1. Pedigree of Paget's Disease (Osteitis deformans).

herited the gene through his mother. So far as the propositus knows, his younger sister exhibits no evidence of the condition.

A survey of the literature suggests that the predisposition to Paget's disease, when inherited, is transmitted as an incompletely dominant gene carried on an X-chromosome.

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Hereditary Congenital Macular Degeneration[1]

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INTRODUCTION

THE area centralis of the retina is a rod-free, cone-bearing region of the retina at the posterior pole of the eye, serving as an area of maximal acuity of form and color perception. In man and other primates the area is diffusely stained with a yellow pigment and is known as the macula lutea. This structure is evidently the seat of a great many hereditary modifications, for the various macular lesions described in families vary greatly in their ophthalmoscopic appearance, in the age on onset of the ophthalmoscopic changes and visual symptoms, and in their mode of inheritance. In some forms there is associated mental defect, e.g., the "cerebromacular diseases". In the present paper the discussion will concern itself with one of the less well-known forms of macular dystrophy, a type resembling most closely the "congenital macular degeneration" first described by Best (1905).

In 1905 Best reported a family containing 8 affected members among 59 examined individuals. Best described the defect as "familial congenital macular degeneration". No case, however, was seen at or near birth. In this family the abnormality of the fundus was confined to "a bright red, round, sharply delimited center or an inactiv choroiditis. The lesions always lie directly under the fovea". Further points of distinction brought out in the paper were: 1) non-progression of the macular change, 2) common association with hypermetropia, and 3) usual retention of good central vision despite the extensive ophthalmoscopic changes.

Further studies of this family were reported by Vossius (1921), Weisel (1922), and Jung (1936). A total of 300 individuals were observed, of whom 22 were considered affected. Two cases showed unilateral involvement only, and colorblindness was reported in one affected member. The mode of inheritance was irregularly dominant, as was pointed out later by Franceschetti. These later investigations showed that some of the macular lesions actually did progress. In one individual the macular alteration did not make its appearance until after the second dentition, showing that the age of onset may be variable.

The literature contains few reports of macular defects of a similar nature. Best himself was unable to find additional reported families. He did, however, mention the relationship of his observations to those macular lesions sometimes seen in cases of congenital total colorblindness. Kurz (1947) observed an intense yellow staining of the foveal area in a 43 year-

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old man and in 2 of his daughters. This author assumed that there may have been a failure of involution of the embryonal layer of Chievitz.

Riser, McFarland and Klien (1948) recently observed a family almost identical to the author's. At the 1948 Chicago meeting of the American Academy of Ophthalmology and Otolaryngology, Dr. Riser presented colored slides of several of the younger affected members of his family, showing macular lesions having the appearance of "an egg with the sunny side up". Berkley and Bussey (1949) have also described a family with an irregularly dominant form of macular degeneration similar to the family which will now be described.

REPORT OF A FAMILY

A hitherto undescribed kindred possessing hereditary macular degeneration (University of Michigan Heredity Clinic No. 1093) is shown in figure 1. The

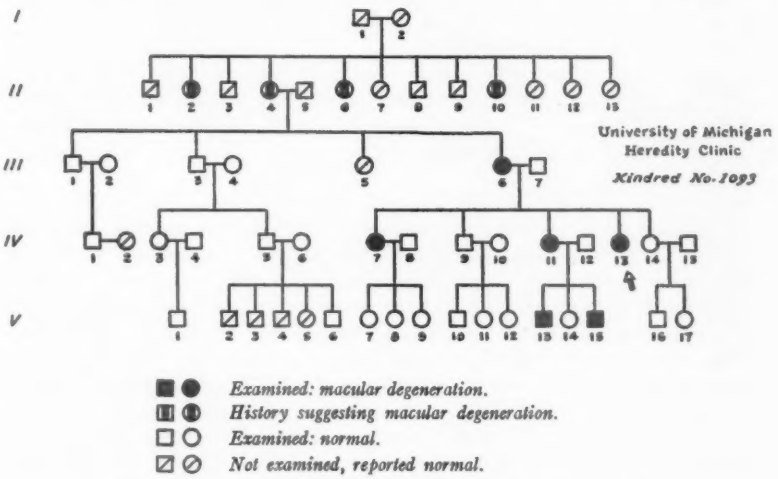

FIG. 1. Pedigree of congenital macular degeneration (Best's type).

proposita, *IV-13*, was first seen in 1947 at age 36 years. She complained of ocular discomfort while reading and had a very short span of ocular attention. Both maculae showed conspicuous degenerative changes. Investigation of this woman's relatives revealed similar abnormalities in her mother, in two of her sisters, and in two nephews. In addition, there was a history suggestive of macular degeneration in the maternal grandmother and in three of the latter's sisters. The family is chiefly of Scotch and English stock and has resided in central Michigan for at least four generations.

There was no evidence of mental defect or psychic disturbances in any affected or unaffected member of the family examined. In fact, the level of intelligence in all six individuals showing macular degeneration seemed well above average. Because of the variability in funduscopic findings, visual

symptoms, and other ocular manifestations, each case will be summarized separately.

DESCRIPTION OF AFFECTED MEMBERS

The inclusion of *II-2*, *II-4*, *II-6* and *II-10* on the pedigree as affected individuals is based entirely on hearsay evidence furnished by *III-6*. *II-4*, the mother of *III-6*, had been known to be incapable of performing fine, discriminative visual work since her early thirties. Reading, sewing and writing were not possible despite frequent changes of glasses. *II-2* developed poor visual acuity shortly after leaving grammar school. She was never able to do detailed visual tasks. *II-6* developed visual difficulty in her early twenties, characterized chiefly by inability to read and write. *II-10* is reported to have had poor vision to the extent that she always had her children read and write letters for her.

III-6. This frail 68 year-old housewife reported that she had first become conscious of visual acuity loss at the age of 14½ years. At that time she was told by her local ophthalmologist that she would eventually be blind.

The patient's uncorrected and corrected visual acuity was 2/60 in the right eye and 4/60 in the left eye. She could not read any Jaeger type. The eyes were essentially straight in the primary position. Fixation was slightly eccentric in each eye. External and slit-lamp examinations of the anterior ocular segment revealed only arcus senilis and a few corneal guttata bilaterally.

Funduscopic examination. Right eye: The lens was clear except for a few cuneiform opacities in the nasal half. A few vitreous opactities were present. The disc was oval vertically and of fair color. The retinal arteries were sclerotic and tortuous. The macular area presented a horizontally oval patch of atrophy of slightly greater than disc diameter size. The atrophic area was moderately depigmented but showed scattered densely clumped pigment strands on the surface. Some glial infiltration of the central area made visualization of the choroidal vasculature impossible. The retinal periphery appeared normal throughout (fig. 2). *Left eye:* The changes were similar to those of the right eye with the exception of the macular alteration. A zone of atrophy occupied the macular area. Rather extensive glial and scar proliferation was present within the central portion of the atrophic depigmented area. Careful scrutiny revealed an occasional bared choroidal vessel. Scattered about in the paramacular area, especially inferiorly, were several rather large colloid-like bodies or hyaline deposits.

Refraction—(cycloplegic). *Right eye:* +1.25 sph., +0.37 cyl., axis 180°, visual acuity 2/60. *Left eye:* +1.50 sph., +0.50 cyl., axis 176°, visual acuity 4/60.

Tonometer Tension: 22 mm. Hg. bilaterally. (New Schiøtz).

Visual Fields (3/1000 test object). Peripheral fields were normal; centrally there was a small absolute paracentral scotoma in each eye. Fixation was eccentric in each eye.

Color vision was definitely normal (Ishihara, Farnsworth 100-Hue) (see fig. 3).

IV-7. This large, dark-complexioned, 43 year-old female related that she had always had "trouble with her eyes". She had first worn glasses at the age of 11. Definite visual loss was experienced in the left eye at the age of 25 years. Intensive therapy, as well as eradication of all foci of infection, was instigated for "central choroiditis" in both eyes at that time.

The uncorrected visual acuity was 6/6 in the right eye and 2/60 in the left eye, with correction 6/6 right eye, and 2/60 left eye. Jaeger O type could be read with the right eye and Jaeger 14 type poorly with the left eye at 13 inches. There were 8–10 degrees of left divergent strabismus. The remainder of the anterior ocular segment findings were normal in each eye.

Funduscopic examination. Right eye: The lens and central media were normal. The optic nerve, retinal vasculature and retinal periphery were without alteration. The macular area

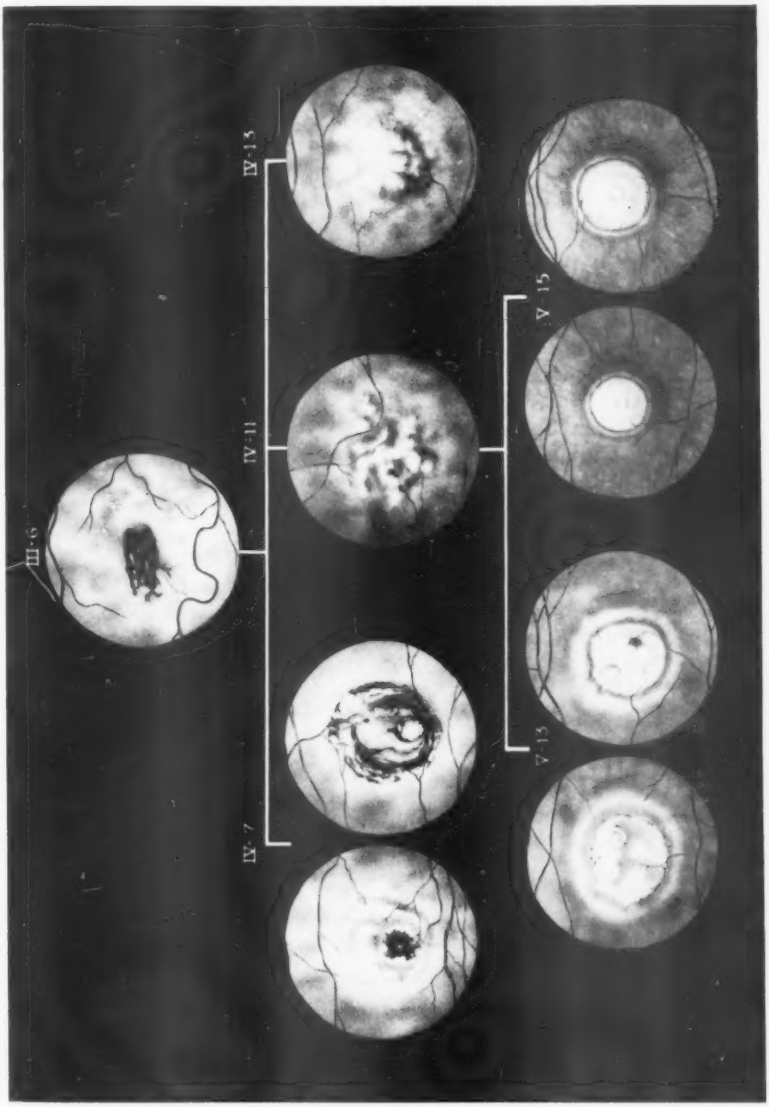

FIG. 2. Macular lesions in six affected members of a family possessing congenital macular degeneration. Illustrations by Janet McLaughlin. [Falls, H. F. 1949. *Am. J. Human Genet.* 1(1): 96–104.]

and the immediate neighborhood revealed a dirty yellowish-grey zone of depigmentation, somewhat elevated, and apparently having an irregular surface contour. The foveal area was replaced by an extensive blob of dense black pigment. Scattered about the macular and paramacular zones were several large colloid-like bodies. *Left eye:* The macular changes closely simulated those of the right eye; yet there were conspicuous differences. A rather large oval area of macular atrophy was present in which the pigmentation was rather extensive. The latter was arranged in curved linear or arc-like streaks and clumps (fig. 2). The entire central area was surrounded by a grey zone or halo of depigmentation, as if the lesion was advancing peripherally. Central colloidal bodies could be seen through the less densely pigmented areas.

Refraction (cycloplegic). *Right eye:* +1.50 sph., +0.25 cyl., axis 95°, visual acuity 6/6. *Left eye:* +1.50 sph., 0.00 cyl., visual acuity 2/60.

Visual Fields as tested with the perimeter were normal. (2/330 test object). With the Bjerrum Screen, a small central absolute scotoma was demonstrated (3/1000 white test object) in each eye.

Color vision tests (Ishihara, Farnsworth 100-Hue) showed a moderate degree of "low discrimination".

IV-11. This stockily built, sandy-haired 36 year-old female was persistent in her complaints of ocular discomfort. She felt that her asthenopia had been more severe during the past two years.

The corrected visual acuity was 6/6 −2 in the right eye and 6/9 in the left eye, with correction 6/6 −3 right eye and 6/9 +2 left eye. The muscle measurements were normal, and the external and slit-lamp examinations revealed normal anterior ocular segments.

Funduscopic examination. Right eye: The lens and central media were normal. The disc was oval in shape and normal in color. The macular area was questionably elevated. Centrally, there was a rather extensive greyish glial infiltration superimposed on numerous irregular greyish-yellow discrete and conglomerate colloid bodies. The entire macular zone, between the temporal vessels, was slightly depigmented, presenting a moth-eaten appearance, with scattered large and small colloid masses. The retinal vasculature and periphery were without abnormality. *Left eye:* The fundus showed changes similar to those of the right fundus, except that there was less central glial infiltration. The paramacular area was atrophic and slightly depigmented with a peculiar beaten-bronze, glistening appearance. The central area presented discrete and conglomerate colloid masses with some superficial pigment clumping as illustrated in the drawing (fig. 2). Several colloidal bodies, large and small, were present in the paramacular area. The retina was otherwise normal.

Refraction: (cycloplegic). *Right eye:* +2.75 sph., +0.25 cyl., axis 180°, visual acuity 6/6 − 2. *Left eye:* +2.75 sph., +0.50 cyl., axis 15°, visual acuity 6/9 +.

Visual Fields as tested with the perimeter, were within normal limits for each eye. Central fields (Bjerrum screen) revealed no scotomata, although the 1 mm. white test object was frequently lost.

Color vision tests (Ishihara, Farnsworth 100-Hue) showed "low discrimination" (see fig. 3).

IV-13. This reddish-haired 36 year-old short, stocky female had no specific ocular complaints other than inability to read comfortably for any length of time.

The corrected visual acuity was 6/6 in the right eye and 6/6 − 2 in the left eye. The near point of accommodation was Jaeger 0 type at 32 cm. in the right eye and 30 cm. in the left eye. There was definite convergence under cover and Maddox rod measurements disclosed 6^{Δ} of esophoria for distant vision and 2^{Δ} of esophoria in accommodation. The external and slit-lamp examinations were otherwise normal.

Funduscopic examination. Right eye: The disc, retinal vasculature and periphery were

normal. The macular area was replaced by a superficial greyish-white glial infiltration of irregular density and distribution. Discrete and conglomerate yellowish-grey colloid bodies could be seen beneath this glial veil. Very fine pigment clumping and stippling could be seen at and about the borders of the lesion. The paramacular area appeared moderately depigmented in a moth-eaten manner. Scattered yellowish-grey colloid bodies were also present in the latter zone. *Left eye:* As in right eye, (see drawing, fig. 2).

Refraction (cycloplegic). *Right eye:* +6.00 sph., +0.25 cyl., axis 116°, visual acuity 6/6 − 1. *Left eye:* +6.00 sph., +0.25 cyl., axis 0°, visual acuity 6/6 − 1.

Visual Fields: Central and peripheral visual fields were normal in each eye. Small white and colored test objects would be lost momentarily on Bjerrum screen, but no definite scotomata could be outlined.

Color vision tests (Ishihara, Farnsworth 100-Hue) showed "low discrimination" of moderate degree.

V-13. This brown-haired male of 7 years had no specific ocular complaint other than inability to attend for any period of time to specific ocular tasks.

The uncorrected visual acuity was 6/6 in the right eye and 6/9 − 2 in the left eye. The external examination, muscle measurements and slit-lamp findings were normal.

Funduscopic examination. Right eye: A raised, rather sharply circumscribed, yellowish gelatinous central macular mound was present—"an egg with the sunny side up". This simulated very closely the changes seen in *V-15* except in this eye the lesion was larger and possessed a yellowish-grey halo. In the center of the lesion were a few areas of more intense yellow. Pigment stippling and clumping near the periphery or edge of the lesion was a distinction not seen in *V-15*. *Left eye:* As in right eye with but little modification (see diagram, fig. 2).

Retinoscopy (cycloplegic). *Right eye:* +0.75 sph., +0.25 cyl., axis 135°, visual acuity 6/6 +. *Left eye:* +0.50 sph., 0.00 cyl., visual acuity 6/9 − 3.

Visual Fields: Normal except for questionable small relative central scotoma of the left eye, as tested with a 2/1000 red test object.

Color vision tests (Ishihara, Farnsworth 100-Hue) showed "low discrimination".

V-15. This well developed, stocky, reddish-haired 3 year-old male was seen at my request. He had presented no visual complaints.

The external and slit-lamp examinations presented no anterior ocular segment abnormality. The uncorrected visual acuity was 6/15 ± in each eye (E chart).

Funduscopic examination: Right eye: Almost exactly in the macular area there was a raised, circular, gelatinous, greyish-yellow mound, having a rather sharply circumscribed border. The retina at the border appeared taut and raised, presenting numerous highlights to the observer. In the center of the mound there appeared a much smaller crater-like depression. No pigmentation was noted nor were there any scattered colloid bodies. The optic disc, vessels and retinal periphery were without abnormality. *Left eye:* A lesion, similar to the macular change of the right eye, was present although slightly larger and possibly a disc diameter in size (fig. 2).

Retinoscopy (cycloplegic). *Right eye:* +2.00 sph., +1.00 cyl., axis 107°, visual acuity 6/9 − 2. *Left eye:* +2.00 sph., +1.00 cyl., axis 82°, visual acuity 6/9 + 2 (E chart).

Visual fields could not be tested.

Color vision was normal (Ishihara).

DISCUSSION

The inheritance is evidently due to a "dominant" gene in this family. Very likely the factor is on an autosome, although the possibilities of dominant

sex-linked or partially sex-linked inheritance cannot be excluded, since no children of affected males have yet been studied. Cases of unilateral macular degeneration and instances of skipping of a generation ("lack of penetrance") were not observed in this family, in contrast to those reported by Best and others and by Berkley and Bussey.

It is postulated that the macular defect is congenital in origin in this family. The presence of lesions in a 3 year-old male (*V-15*) having no ocular complaints is, however, the sole basis for this contention. Very possibly the age of onset of macular changes may vary considerably, as was hinted in Best's family. It is also suggested that the alteration is a progressive one in that *V-13* has exhibited an increase in pigment clumping and development of additional paramacular white lines and spots during the course of the past two years. Small central absolute scotomata were demonstrated in the two oldest females. Preservation of good visual acuity, however, is the rule in the family, illustrating that visual function may be surprisingly good even when gross ophthalmoscopic changes are present. The association with hypermetropia is self-evident, the errors varying from +0.50 to +6.00 diopters.

There is little doubt that some forms of hereditary macular degeneration are accompanied by defective color vision. From the published accounts, however, it is usually impossible to ascertain whether the defect is a result of the macular lesion or a coincidental occurrence of one of the common forms of sex-linked dichromatism or incomplete trichromatism. In Best's family one case of macular degeneration with "total colorblindness" is recorded. Berkley and Bussey state that colorblindness was observed in their family but do not indicate which members were involved. In the present family, color vision was tested by means of Ishihara (7th edition) plates and the Farnsworth-Munsell 100-Hue test, using a standard Macbeth Type C illuminant for both tests. No cases of red-green blindness were encountered, but 4 of the 5 tested persons having macular degeneration showed reduced color discrimination as revealed by the Farnsworth test. Two of the color vision profiles are shown in figure 3; that of *III-6* shows only a normal number of errors, while that of *IV-11* shows a typical "low discrimination" pattern, with errors uniformly distributed throughout the spectrum. The errors of *IV-7*, *IV-13* and *V-13* were similar to those of *IV-11*, but somewhat less pronounced. These results can hardly be regarded as conclusive evidence of an effect of the macular lesion upon color vision. However, if such an effect exists it is evidently a mild and variable one, as is true of the effect upon total visual acuity.

It is indeed unfortunate that pathological studies are not available. Any attempt to explain the ophthalmoscopically visible changes can thus only be speculative. If I may be permitted such speculation, however, I would suggest that the primary alteration is most likely in the choriocapillaris, in view of the preservation of good visual acuity in most of the affected members of

the family. At first I felt that mild transudation of subretinal fluid from the choriocapillaris had effected a flat detachment of the macula, especially suggested by the appearance of the lesions in the two youngest cases, *V-13* and *V-15*. Slow-acting, mild sub-oxidation and deficient nutrition were presumed to produce the hyaline and colloid-like changes and glial infiltration visualized in *IV-11* and *IV-13*. With the passage of time, there is finally brought about a degeneration of the cones with accompanying pigmentary changes, as seen in *IV-7* and *III-6*. That the hypothesis of primary subretinal transudation may be wrong, however, is suggested by the very early and severe visual loss seen in senile disciform macular degenerations.

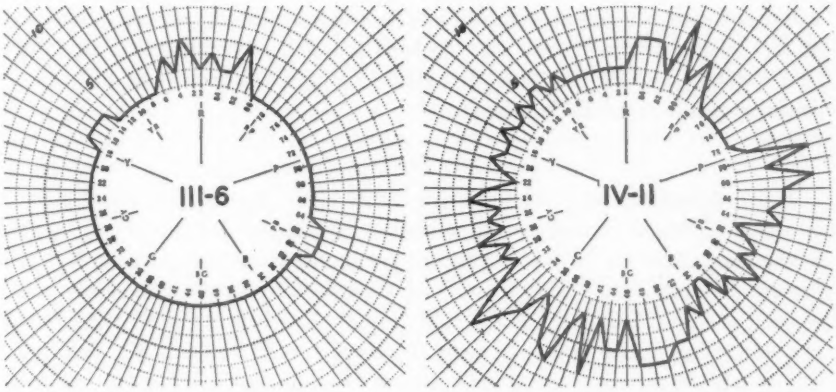

FIG. 3. Color vision profiles (Farnsworth 100-Hue Test, both eyes) on two subjects showing macular degeneration. *III-6* shows a normal number of errors; *IV-11* shows low color discrimination.

Extensive classifications of the degenerative macular diseases, based upon various characteristics of the disease process, have been attempted by various authors. Thus, in 1909, Stargardt recognized four types of macular degeneration, differentiated by clinical appearance, age of onset, and presence or absence of accompanying psychic disturbances. In 1920, Behr classified a number of "heredodegenerative" diseases of the macula according to age of onset, restricting his classification to lesions involving the macula lutea alone. He emphasized that the periods of physiological stress in the life of the individual are the times when macular dystrophy is most likely to begin. With the discovery of more and more intermediate types and with the appearance of an increasing number of genetic studies, it has become apparent that great variability can be expected both within and between families in almost all features of the disease (Sorsby, 1940). Dominant, recessive and sex-linked patterns of inheritance have been observed in both juvenile and adult forms of macular degeneration. Further detailed studies, utilizing all possible information which

can be brought to bear by the ophthalmologist, biochemist, pathologist, embryologist and geneticist will undoubtedly be needed before a sound basis for classification can be expected.

In the meantime, genetic studies have revealed two facts of practical importance. In the absence of a satisfactory etiologic classification and specific means of therapy, the services of the ophthalmologist can be directed towards the problems of predicting the expected clinical course of the disease in the individual patient and its genetic course in different branches of the patient's family. In the former respect, the great variability in manifestation of genes affecting the macula, which, however, usually show somewhat less variability within families, means that a study of several affected relatives of the patient will usually provide a much better basis for prognosis of the course and extent of the disease. Secondly, the varying modes of inheritance make it essential that a detailed ocular study of the patient's family be carried out before eugenic prognosis or advice is offered.

SUMMARY

Macular degeneration is described in a Michigan family in which it shows unbroken dominant transmission through three observed generations. In the 6 examined cases the lesions are rather symmetrical and are presumed to be present at birth. In all cases there is an associated hypermetropia. Retention of good or fair visual acuity is the rule. A questionable and variable reduction in color vision acuity is also present. In these several respects the defect in this family resembles most closely a form of dominantly inherited macular degeneration originally described by Best and likewise considered by him to be congenital.

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UNDER the above title the *Journal* will publish with each issue a bibliography of current research articles and books of interest to students of human heredity. These will be listed alphabetically by author and arranged in sections according to the year of publication (not necessarily the date of issue, in the case of some periodicals). The present list includes titles dating from January 1, 1949. Abbreviations used for the titles of medical serials are those which have been adopted by the U. S. Army Medical Library, as published in the *Index-Catalogue of the Library of the Surgeon General's Office*, Fourth Series, volume 10, and in the *Current List of Medical Literature*.

In order to make the bibliography of greater service, the address of each author, when known, is added in brackets following the citation. Except as otherwise noted, the address is that of the senior author in cases of multiple authorship. When two or more papers by the same author are listed, the address will be found at the end of the first reference cited.

The Editor would appreciate receiving notices of books and papers which have been overlooked, so that these may be included in later lists.

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